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Proceedings of the Conference on Noninvasive and Invasive Prospective Monitoring for Anthracycline Cardiotoxicity

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Proceedings of the Conference on Noninvasive and Invasive Prospective Monitoring for Anthracycline Cardiotoxicity

Division of Cancer Treatment, National Cancer Institute
and
Adria Laboratories

Editors: C. E. Myers
W. P. McGuire

September 19, 1977
Bethesda, Maryland

Prospective Monitoring for Anthracycline Cardiotoxicity: An Introduction

William P. McGuire [1,*]

Since the introduction of the anthracycline antibiotic, adriamycin (ADM), into clinical trials in 1970, two important observations have been made which have spawned this meeting. First, ADM has exhibited a very broad range of activity in several solid tumors including carcinoma of the breast (1), lymphoma (1), carcinoma of the endometrium (2), thyroid carcinoma (3), and bladder carcinoma (4). Not only have these tumors responded to ADM, but responses have been of sufficient duration to allow administration of multiple doses so that the second observation, delayed cardiomyopathy, was possible. Lefrak et al (5) first reported this phenomenon in 1973 and since that time numerous investigators have verified a dose-related pump failure approaching an incidence of 10% at cumulative doses > 550 mg/m^2.

It would seem appropriate, therefore, to simply limit the dose of this agent to avoid the toxic manifestations altogether. Most clinicians, however, have been faced with the difficult decision of discontinuing ADM in a patient who continues to respond to the drug or risk the often fatal cardiomyopathy with further therapy. Unfortunately, the cardiomyopathy is usually progressive and irreversible after the onset of symptoms despite intervention with cardiotonic drugs and/or mechanical circulatory assistance (5).

Thus, many clinicians in various disciplines have explored means by which a noninvasive or invasive test may be useful in guiding the physician in this difficult decision. Medical oncologists, radiologists, cardiologists, and clinical pharmacologists have conducted tests ranging from the simple electrocardiogram to the difficult transvenous biopsy of the endocardium in an effort to find some method to determine if a given patient is capable of receiving further ADM without undue cardiac dysfunction. This symposium presents reports of most of the published and/or ongoing trials in both experimental animals and cancer patients. The meeting is timely because as the clinical spectrum of ADM activity continues to expand, larger numbers of patients will be exposed to this useful, yet toxic, agent. Even more important is the evolution of adjuvant therapy in the cancer patient with earlier stages of disease. In this setting there will certainly be an absolute necessity for determination of a risk/benefit ratio since 5-year postoperative survivals will be the rule rather than the exception.

Lastly, as new anthracycline analogs are developed, there will be a need in both preclinical and phase I clinical trials to determine whether or not a new analog has an increased therapeutic ratio over the parent compound. Only with some predictive test or biochemical assay will this be possible without unnecessarily subjecting the cancer patient to a premature death from anthracycline-induced cardiomyopathy and congestive heart failure.

We hope this meeting will produce the necessary information and ideas to find a way to administer this active class of drugs to maximal tolerance without toxicity.

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Invasive and Noninvasive Methods of Assessing Adriamycin Cardiotoxic Effects in Man: Superiority of Histopathologic Assessment Using Endomyocardial Biopsy [1]

Jay W. Mason,* Michael R. Bristow, Margaret E. Billingham, and John R. Daniels [2]

SUMMARY

Endomyocardial biopsies and cardiac catheterizations were performed in 55 patients treated with adriamycin (ADM). Eleven patients underwent serial invasive studies. In addition, most of these patients had systolic time interval determinations, echocardiograms, and electrocardiograms at the time of catheterization. The relationship of these various tests to cumulative dose of ADM and to the incidence of cardiac dysfunction was analyzed. Only pathologic assessment of ADM-induced myocardial damage showed a progressive stepwise increase in severity at successively higher doses of ADM. In addition, the incidence of myocardial dysfunction correlated well only with pathologic findings on biopsy. We conclude that standard noninvasive methods of assessing ADM cardiotoxicity are inadequate and that histopathologic assessment by means of endomyocardial biopsy is a valuable, reliable, and accurate technique.

[Cancer Treat Rep 62:857–864, 1978]

Cardiotoxicity limits the usefulness of adriamycin (ADM) in the treatment of human neoplasms. As a result of early, retrospective studies, clinicians have learned to avoid cardiotoxicity in most patients by limiting the cumulative dose of ADM to 550 mg/m^2 (1,2). However, there is considerable variation from individual to individual in cardiac tolerance to ADM. In addition, certain risk factors, including prior cardiac disease, advanced age, and previous mediastinal radiation therapy, promote the development of ADM cardiotoxicity at lower dose levels (3–5). Because some patients may require > 550 mg/m^2 of ADM, and because other patients may develop heart failure from ADM at dose levels < 550 mg/m^2, accurate methods of assessing the degree of ADM-induced cardiac injury are sorely needed by the clinician. Serial measurement of the electrocardiographic (ECG) voltage (6), echocardiography (7), and systolic time interval determinations (8) have been utilized by various investigators. Although results by these three methods have yielded some correlation with the cumulative dose of ADM, none of these methods have been effective in quantitating the severity of ADM heart disease, and none of them can be relied upon to accurately predict an individual patient's ability to tolerate further ADM therapy.

By means of light and electron microscopic study of endomyocardial biopsy specimens obtained from patients treated with ADM, we have recently described specific myocyte abnormalities (9). We have demonstrated that these myocyte abnormalities can be quantified to measure the severity of ADM cardiotoxic effects in man (3). This report deals with endomyocardial biopsy, cardiac catheterization, and ECG, echocardiographic, and phonocardiographic findings in 55 patients treated with ADM. The purpose of this communication is to compare the worth of the above-mentioned noninvasive techniques with the biopsy-histopathologic technique of assessing ADM cardiotoxic effects in man.

MATERIALS AND METHODS

Sixty-seven endomyocardial biopsy procedures and cardiac catheterizations were performed in 55

[1]Supported in part by a grant from Adria Laboratories (Wilmington, Del), and by Public Health Service grant CA-05838 from the National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare.

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patients aged 19 to 78 years (mean age, 43 years) treated with ADM. During the initial period of this study, patients were asked to participate in a protocol to evaluate cardiac histopathology in patients receiving ADM. These patients signed informed consent to participate in the research investigation. In the latter portion of this study, patients underwent biopsy and catheterization to determine if they had ADM cardiotoxicity or if they could receive further ADM therapy, since the biopsy technique had already been validated. Ten patients had two serial biopsy and catheterization procedures and one had three. Prior to all of the invasive procedures, ECGs were recorded. Fifty-one systolic time interval determinations and 37 percent fractional shortening (FS) measurements by echocardiogram were obtained immediately prior to the invasive procedure.

Right ventricular endomyocardial biopsies were performed by a previously described technique (10). A 9-French catheter bioptome, 50 cm in length, was introduced percutaneously through the right internal jugular vein and advanced across the tricuspid valve to the apical portion of the right ventricular septum where three or four tissue samples were obtained. Endomyocardial samples were usually 2 mm in diameter. One sample was placed in 10% buffered formalin and one or usually two samples were preserved in 2.5% gluteraldehyde. An additional sample was rapidly frozen in isopentane and dry ice for long-term storage. The formalin-preserved specimens were sectioned and stained with hematoxylin and eosin and Masson's trichrome stain for light microscopy. The gluteraldehyde specimens were post-fixed in cold 1% osmium tetroxide, stained en bloc with 2% uranyl acetate, and embedded for sectioning for electron microscopy.

Systolic time interval determinations were made using a sound transducer placed in the second left intercostal space and an external carotid pulse wave microphone, both recorded simultaneously with lead II of the surface ECG at a paper speed of 100 mm/second on an Irex multichannel recorder according to standard techniques (11, pp 21–34). The pre-ejection period (PEP) was defined as the difference between the interval from onset of the Q wave in the ECG to the onset of the aortic component of the second heart sound (Q-S_2), minus the left ventricular ejection time (LVET), defined as the time interval from onset of the upstroke of the carotid pulse tracing to the dicrotic notch: PEP = Q-S_2–LVET. The ratio of the PEP divided by the LVET was determined in each patient when technically adequate tracings were obtained. Normal values and use of this index as a measure of left ventricular function have been previously reported (11, pp 167–169).

Twelve-lead ECGs were obtained prior to each invasive procedure. Tracings were obtained at the same time of day in each patient by one of two technicians using the same Hewlett-Packard electrocardiograph precisely standardized at 10-mm deflection = 1 millivolt. The summated ECG voltage was measured by adding the total deflections in millimeters of the largest QRS complex in each of leads I, II, III, V_1, and V_6. Care was taken in accurate placement of the chest leads. This method of voltage measurement was selected because it was developed in the Stanford Cardiac Transplantation Program and it is the only technique of which we are aware that has been clearly shown to demonstrate predictable serial changes during the development and resolution of a myocardial disorder (in this instance, cardiac rejection; ref 12).

Echocardiograms were recorded using a 2.25-MHz transducer connected to a Smith Kline Model 20A echograph and recorded on an Irex multichannel recorder. The echocardiographic percent FS was defined as the left ventricular internal diameter in diastole, measured just prior to the onset of the QRS complex, minus the left ventricular internal diameter in systole, measured at the peak of the anterior motion of the left ventricular posterior wall, divided by the left ventricular internal diameter in diastole:

$$\frac{LVID_D - LVID_S}{LVID_D} \times 100 = \% \text{ FS}.$$

Following right ventricular endomyocardial biopsy, right heart catheterization was performed in each patient. Resting hemodynamic recordings were made and resting Fick cardiac output was determined. Then, 15 of the patients performed supine bicycle exercise during which repeat hemodynamic determinations and Fick cardiac outputs were done. Catheterization abnormalities used as evidence of cardiac dysfunction were defined as follows: resting cardiac index < 2.5 liters/minute, exercise factor (change in cardiac output divided by change in oxygen consumption during exercise) < 5, resting pulmonary artery wedge mean pressure > 12 mm Hg, resting right ventricular end diastolic pressure > 12 mm Hg, and a rise in pulmonary artery wedge mean pressure of > 10 mm Hg above the resting level recorded with the patient's feet elevated and strapped to the bicycle pedals. A clinical diagnosis of congestive heart failure, corroborated by chest roentgenographic findings and physical examination by the group's cardiologist, was also accepted as evidence of cardiac dysfunction.

Our system for grading of the severity of ADM cardiotoxicity has been previously described (3,5). Biopsies showing no evidence of ADM cardiotoxicity are scored 0. Severe diffuse changes are scored 3+. Scores of 1+ and 2+ indicate intermediate severity of cardiotoxic change. Biopsies of 1+ show single or only a few scattered areas of pathologic change and 2+ biopsies show more diffuse and severe changes.

RESULTS

Cardiovascular Findings Related to Cumulative ADM Dose

Figure 1 shows bar graphs relating the PEP:LVET, the %FS on the echocardiogram, and the pathology score related to the cumulative dose of ADM. Patients are separated on these graphs according to whether or not they had had significant prior mediastinal radiation therapy. Figure 1a demonstrates that the PEP:LVET, which is said to increase in patients with cardiac dysfunction (12), in fact shows no predictable relationship with cumulative ADM dose in either the radiated or nonirradiated groups. In fact, the ratio tended to be somewhat higher (that is, *more* abnormal), though not statistically significantly higher, in patients with lower ADM doses, which is contrary to what one would expect if this test were sensitive in demonstrating the cardiotoxic effects of ADM. Figure 1b reveals that the FS value on echocardiogram also showed no specific relationship to cumulative ADM dose. On the other hand, figure 1c demonstrates that the pathology score tends to be higher (more abnormal) at higher cumulative dose levels of ADM. Indeed, the mean pathology score, especially in the irradiated patients showed a stepwise increase at successive dose levels. However, there was considerable overlap in biopsy scores at each ADM dose range, as indicated by the wide standard deviations.

Relationship of Noninvasive and Pathologic Findings to the Incidence of Cardiac Dysfunction

In figure 2 the incidence of cardiac dysfunction, as judged by clinical findings or catheterization abnormalities, is related to noninvasive and biopsy findings. Figure 2a reveals only a small difference in the incidence of cardiac dysfunction in patients with normal systolic time interval values (PEP:LVET < 0.38) and patients with markedly abnormal values (PEP:LVET > 0.45), the former group having a 31% incidence and the latter group a 33% incidence of cardiac dysfunction. Figure 2b shows no gradual increase in the incidence of cardiac dysfunction at progressively lower (more abnormal) percent FS values on echocardiogram. Only at markedly abnormal values (FS $< 30\%$) is there a clear increase in the frequency of cardiac dysfunction (58%). In figure 2c the incidence of cardiac dysfunction is shown at each dose range. This analysis reveals evidence of myocardial failure even at low cumulative dose levels of ADM. Once again, one does not see a stepwise increase in cardiac dysfunction at each dose range, although there is a higher incidence at the highest dose levels than at the lowest dose levels. Chi-square analysis revealed no significant differences in the incidences of cardiac dysfunction between any of the PEP:LVET or percent FS value ranges or between the cumulative dose intervals. The high incidence of cardiac dysfunction in this analysis is not indicative of an unusually high rate of *overt* congestive heart failure in our patients, but it does suggest that latent cardiac dysfunction, detectable by cardiac catheterization, is common in patients receiving ADM, even prior to their attainment of high cumulative doses. Only nine patients in this series had clinically overt and symptomatic congestive heart failure.

Figure 2d shows a regular stepwise increase in the incidence of cardiac dysfunction with higher biopsy scores. One patient with a biopsy score of 0, who had received 125 mg/m^2 of ADM, had congestive heart failure, but this was a result of a previous large inferior wall myocardial infarction with associated chronic mitral regurgitation. Chi-square analysis revealed significant differences ($P < 0.01$) in the incidence of cardiac dysfunction in patients with 3+ biopsies compared to those with 0 and 1+ biopsies. Thus, the pathology score, used as a method of direct assessment of ADM-related myocardial damage, clearly shows the best correlation with cardiac dysfunction in this group of patients.

Serial Investigations

Eleven patients underwent at least two endomyocardial biopsy and catheterization studies during the course of therapy. In addition, serial systolic time interval determinations, echocardiograms, and ECGs were available in most of these patients. Figure 3 shows the serial change in the measured variables in these patients related to their cumulative ADM doses. In figure 3a it can be seen that the PEP:LVET showed a general trend toward higher values, but for each patient the determination showed considerable unpredictable variation over time.

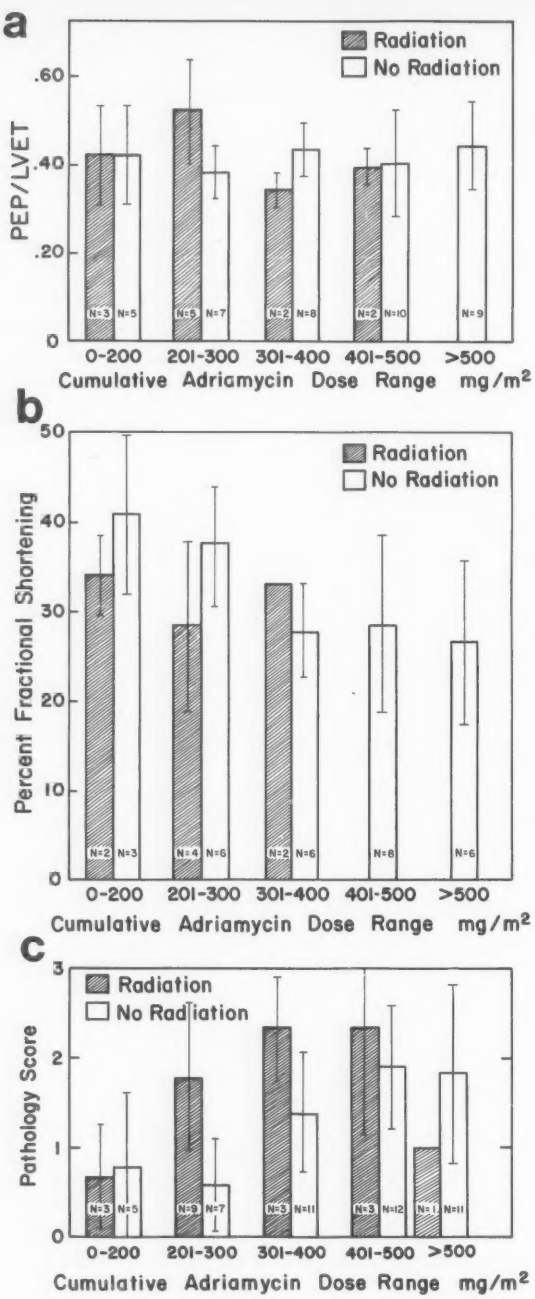

FIGURE 1.—Mean PEP:LVET, echocardiographic % FS, and pathology scores for irradiated and nonirradiated patients are shown at successively higher dose ranges of ADM. N = No. of studies in each category. SDs are indicated. (*a*) Poor correlation of the PEP:LVET with ADM. (*b*) Slight, statistically insignificant decrease in % FS at higher dose ranges. (*c*) Progressive increase in the mean pathology score, especially evident in the irradiated patients, at each dose interval. Wide SD notations indicate considerable individual variations.

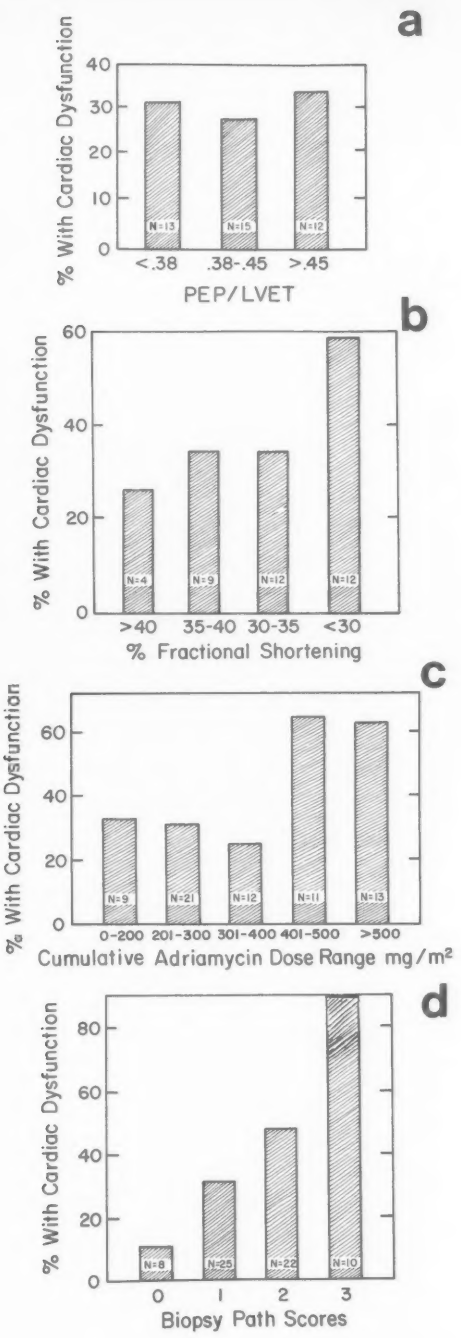

FIGURE 2.—Incidence of cardiac dysfunction, as defined in the text, is related to PEP:LVET (*a*), % FS on echocardiogram (*b*), cumulative dose of ADM (*c*), and pathology score on biopsy (*d*). N = total No. of studies in each interval defined on the abscissa. While trends toward more cardiac dysfunction are present at successively higher values of PEP:LVET, at FS values < 30%, and at ADM dose levels > 400 mg/m², chi-square analysis indicates no statistically significant difference in incidences of cardiac dysfunction in any of the groups of PEP:LVET values or % FS values shown. On the other hand, the incidence of cardiac dysfunction progressively increases in an even, stepwise fashion as the pathology score increases, and chi-square analysis did reveal statistically significant differences in the incidence of dysfunction in patients with 3+ pathology scores compared to those with 0 and 1+ scores.

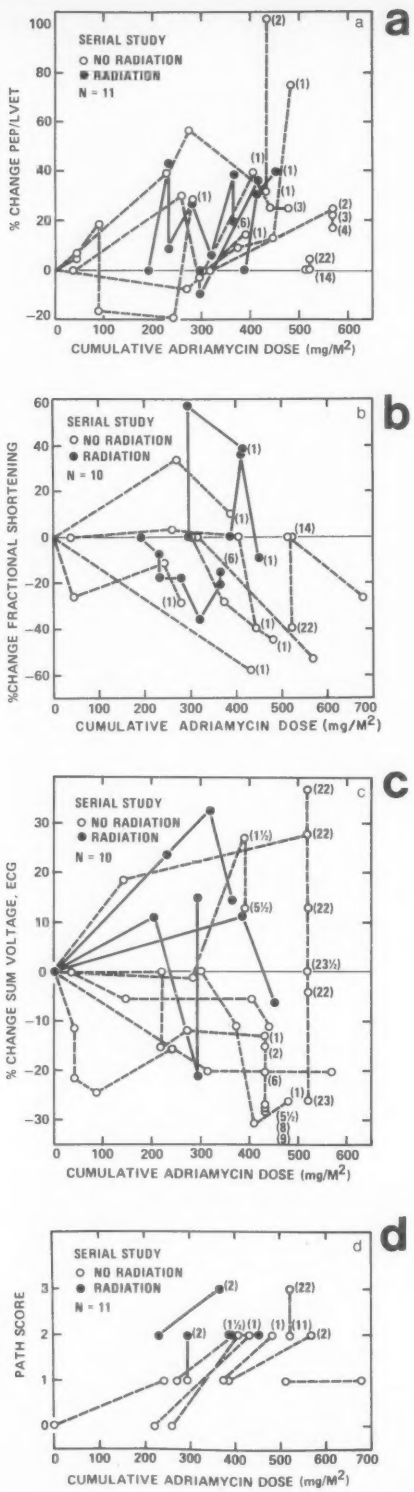

FIGURE 3.—Serial determinations of PEP:LVET (*a*), FS (*b*), summated ECG voltage (*c*), and pathology score (*d*) are shown as % change from the baseline determination in *a* through *c* and as individual pathology scores in *d*. These determinations were obtained from 11 patients who had ≥ 2 endomyocardial biopsies. *a* through *c* reveal that the 3 noninvasive methods do not change in a consistent fashion when multiple measurements are carried out in individual patients over time. On the other hand, the pathology score increased in all but 2 of the patients, and never decreased during continued ADM therapy. The figures enclosed in parentheses refer to the time in mos after the last ADM dose (if that time was > 3 wks) at which the biopsy was obtained.

Figure 3b, which shows the serial echocardiographic percent FS determinations in these patients, demonstrates a phenomenon similar to that seen in the previous panel. The echocardiographic FS did tend to diminish during ADM therapy but there was not a graduated response over time. Two patients showed an increase (improvement) in FS and two other patients showed increases prior to decreases in FS, compared to their baseline determinations, during ADM therapy.

The summated ECG voltage, shown in figure 3c, showed an even more dramatic variability. On the other hand, as shown in figure 3d, the pathology score determined by electron microscopy of biopsy specimens from the heart showed an increase in all but two of the 11 patients. A few additional observations can be noted in figure 3d. One patient received radiation therapy after reaching a cumulative dose of ADM of 300 mg/m^2. This patient showed an increase in pathology score from 1+ to 2+ subsequent to radiation. This occurrence is consistent with our previous finding of radiation enhancement of the ADM-induced cardiac lesion (5). Another patient who had reached a cumulative dose of $>$ 500 mg/m^2 of ADM and who was biopsied for the first time 11 months following the last dose of ADM showed an increase from a score of 2+ to 3+ on his second biopsy, which was obtained a full 22 months after the last dose of ADM. This patient had received no intervening radiation therapy. This observation suggests that, in at least some patients, the ADM-induced lesion can progress without further ADM therapy.

DISCUSSION

The importance of accurately assessing ADM cardiotoxicity in man cannot be overstated. While it is clear that higher doses are more frequently associated with clinically apparent cardiotoxicity in man, some patients will tolerate cumulative doses of ADM far in excess of 550 mg/m^2, while others may develop heart failure prior to this arbitrary dose limit. Thus, numerous investigators have attempted to detect ADM cardiotoxicity in man using various generally noninvasive techniques (6–8). There are two valid reasons for developing accurate toxicity assessment methods: first, to allow safe, individualized therapy with ADM without adherence to an arbitrary dose-limitation level, and second, to establish criteria for measuring toxicity of new anthracycline drugs.

The purpose of the present study was to compare prospectively the accuracy of five methods in current clinical use for assessing cardiotoxicity and gaiting therapy with ADM: ECG voltage measurement, echocardiography, systolic time interval determination, simple cumulative dose calculation, and endomyocardial biopsy.

Since a priori none of these methods could be considered a "gold standard" of comparison, we used cardiac catheterization, including exercise hemodynamic studies, to detect cardiac dysfunction in our patients. While arguments can be offered against the validity of any clinically available test of cardiac function, we felt that right heart catheterization would be the most accurate invasive method which would remain within the limits of patient acceptability and practicality.

Our findings in figure 1, which relates cardiac function assessed by various measurements to cumulative ADM dose, demonstrate that none of the noninvasive methods correlates well with cumulative ADM dosage. Findings in serially biopsied patients (fig 3) corroborate this observation. The lower panels of figures 1 and 3, which relate the pathology score to cumulative dose levels of ADM, demonstrate the best stepwise change of all the assessment methods. However, it is important to note the wide standard deviations of pathology scores at each dose range in figure 1c, and the fact that individual patients in figure 3d show considerable differences in their pathology scores at nearly equal dose levels of ADM. These findings indicated that each individual patient can be expected to show progressive ADM-induced pathologic changes at successively higher dose levels, but that any one patient's degree of changes at a given dose, and the rate at which that change will progress with further treatment, cannot be accurately predicted. In other words, there is considerable variability in patient sensitivity to the cardiotoxic effects of ADM.

To place the value of dose calculations for assessing cardiac toxicity in an even more negative light, our data reveal a poor correlation of cumulative ADM dose with the incidence of cardiac dysfunction (fig 2c). On the other hand, the pathology score showed a clear, evenly graduated increase in the incidence of dysfunction at higher (more abnormal) scores. This relationship to cardiac dysfunction was superior to that shown for all the other variables.

We analyzed serial noninvasive studies in the 11 patients who underwent two or more heart biopsies (fig 3). This analysis offers the important observation that, even in individual patients, phonocardiographic, echocardiographic, and ECG findings cannot be relied upon to detect or to rule out the ADM-induced lesion.

We feel that pathologic assessment of the ADM cardiac lesion has an accuracy at least as good as that of hemodynamic catheterization. Its advantage

over simple catheterization is its specificity. In patients in whom cardiac dysfunction might have additional etiologies (eg, coronary artery disease, radiation-induced myocardial fibrosis, radiation-induced pericardial constriction or effusion, or independent myopathies and valvulopathies), myocardial biopsy offers the only reliable method of quantitating the contribution of ADM cardiotoxicity to the patient's cardiac compromise. The other assessment techniques are either too insensitive or inherently unreproducible. The echocardiographic FS could detect cardiac dysfunction only when considerable compromise was present, while the PEP:LVET showed such unpredictable variability that there was nearly no difference in the incidence of cardiac dysfunction in patients with systolic time interval values in the normal range compared to the markedly abnormal range of the test (fig 2).

While our data offer strong support for the use of endomyocardial biopsy to assess ADM cardiotoxicity in man, two questions regarding clinical applicability of the technique remain. First, can the technique become widely available? Two barriers to this desirable end exist: (*a*) pathologists with the knowledge and equipment to evaluate the lesion histologically are rare, and (*b*) the technique of endomyocardial biopsy is practiced in only a few centers in the world. To overcome these barriers will require considerable time and training.

The second question regarding clinical application of the biopsy technique in patients receiving ADM is as follows: can the scoring system be used to *predict* drug tolerance in individual patients, so that dosage can truly be accurately gaited? Conclusive data to answer this question do not exist. That is, we cannot say in every case that a patient whose pathology score is known at a certain cumulative dose of ADM can receive a specific additional amount of the drug with impunity. However, some information relating to this question does exist. Nine of ten of our patients with pathology scores of 3+ had cardiac dysfunction. Six of them had overt, limiting congestive heart failure, and three of these patients died as a result of cardiotoxicity. On the other hand, no patients with scores of 0 and only one of the 25 patients with scores of 1+ have developed new, overt heart failure without subsequent treatment. The latter patient was > 70 years old, which is a known risk factor for heart failure in patients treated with ADM (3). It would seem safe to say, then, that patients with 3+ scores should not receive additional anthracycline therapy, while patients with 0 and 1+ scores can. *How much* drug the latter patients may safely tolerate is not yet established. The patients who present the greatest difficulty at our current level of understanding are those with 2+ scores. Although we have administered additional ADM to such patients without adverse sequelae, we have generally recommended discontinuation of the drug in patients with 2+ scores. Studies are underway at our center to make dose modulation by use of the biopsy a more scientific process.

We conclude that histopathologic assessment of endomyocardial biopsies is an accurate method of quantifying ADM cardiotoxicity in man. In addition, the severity of pathologic change correlates well with the degree of functional cardiac compromise. Finally, histopathologic assessment is clearly superior to dose calculation, and to echocardiographic, phonocardiographic, and ECG evaluation of the cardiac lesion.

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Anthracycline Cardiomyopathy Monitored by Morphologic Changes[1]

M. E. Billingham,* J. W. Mason, M. R. Bristow, and J. R. Daniels[2]

SUMMARY

Seventy-six endomyocardial biopsies obtained from 60 patients receiving adriamycin (ADM) and other anthracycline analogs were studied. The biopsies were studied by light and electron microscopy. Two main types of myocyte degeneration were consistently present, the lesions were focal, and inflammatory infiltrate was absent. The severity of pathologic changes was graded on a scale from 0 (normal) to 3 (marked abnormality). Twelve patients receiving previous mediastinal irradiation (600–5700 rads) showed a mean pathology grade (2.0 ± 0.89) that was significantly higher than in those patients receiving a comparable dose of ADM but who were not irradiated (1.18 ± 0.23) ($P < 0.01$). This study indicated that radiation, even if remote, enhances ADM-induced cardiotoxicity and evokes a "recall" phenomenon of latent acute irradiation changes. Our data suggest that a specific, progressive, subclinical injury to the heart occurs with anthracycline therapy that cannot be detected reliably by conventional tests. Anthracycline-induced cardiotoxicity in rabbits, monkeys, and dogs shows the same basic cellular lesions as in man. The analogs, adria-DNA and rubidazone, also show lesions similar to those produced by ADM in the human heart. The endomyocardial biopsy is a reliable method for monitoring cardiac damage due to anthracyclines in man.

[Cancer Treat Rep 62:865–872, 1978]

Adriamycin (ADM) is subject to the toxic side effects common to many antitumor drugs (1). Although of high frequency, these effects are generally reversible and manageable except for the cardiotoxicity causing congestive cardiomyopathy. It is now well established that the cardiotoxic effects are dose-related and that a cumulative dose < 500 mg/m^2 yields a very low incidence of cardiomyopathy, whereas in patients receiving a greater total dose, the incidence climbs rapidly (2). The management of cardiotoxicity by the imposition of an arbitrary dose limitation, however, ignores biologic variation and may deny the drug to a patient who could tolerate additional therapy.

The predictive tests to identify those patients at risk for the development of heart failure have, so far, yielded conflicting data. We have approached this problem in a different way by trying to define and grade the morphologic lesions of this cardiotoxicity in man. Since autopsy material usually provides only the end stage lesions, in this study we have made use of the percutaneous transvenous endomyocardial biopsy. This technique was developed at Stanford in 1973 (3–5) for the clinical management of cardiac allograft recipients. We have performed > 1300 endomyocardial biopsies and have developed a considerable experience both in interpretation and in the actual procedure, which is now well established at Stanford. Using this method, we now have the capability of doing serial investigation on the human heart in vivo.

The tissue obtained by endomyocardial biopsy is usually not > 3.0 mm in maximum dimension. The rapidly fixed tissue provides excellent artifact-free myocardium for conventional microscopy as well as optimal tissue for ultrastructural examination (fig 1). Our data interpretation is facilitated by comparison with control biopsies obtained from young adult organ transplant donors with disease-free hearts.

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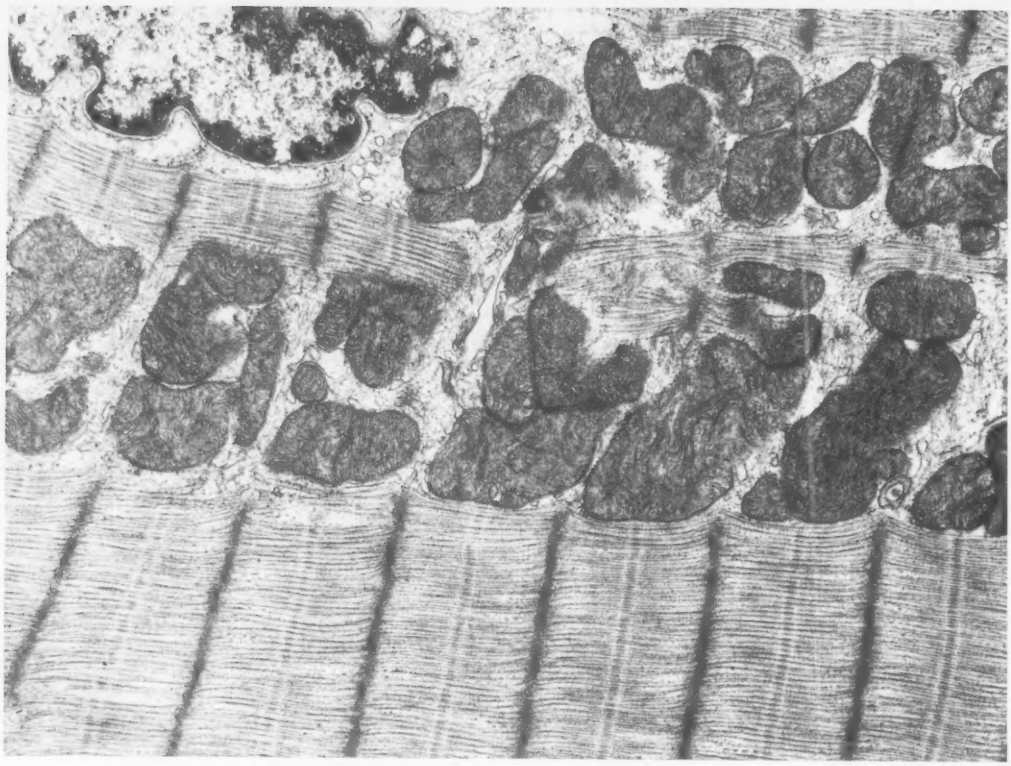

FIGURE 1.—Endomyocardial biopsy of control human myocardium. Original magnification, × 18,750.

The object of this presentation is to propose a new method of monitoring anthracycline-induced cardiomyopathy (6) by grading the severity of the morphologic lesions by light and ultrastructural examination of endomyocardial biopsies. The results leading to this proposal were obtained from 76 endomyocardial biopsies obtained from 60 anthracycline-treated patients aged 19–78 years (table 1). Patients were biopsied with a time lapse varying from 3 weeks to 2 years following their last dose of anthracycline. Fourteen patients had had at least two serial biopsies with an intervening gap of 2 months to 1 year. In addition, 12 patients in the study group had received 600–5700 rads of mediastinal irradiation 6 months to 14 years prior to their anthracycline therapy (table 2).

We found the histopathologic lesions to be both focal and disseminated. In the earliest lesions, single cells with advanced degenerative changes could be seen isolated against a background of morphologically intact myocardium (fig 2). The subendocardium and trabeculae represented a particularly prominent site of involvement in the early stages. Inflammatory infiltrate was not seen even in very severe lesions. Light microscopic changes included an increase in interstitial fibrosis from normal; however, this change is dose-dependent and not always present. There are two main types of myocyte injury which occur. The first is myofibrillar loss which is partial to begin with but which may become total (fig 3). In the myocytes affected this way, the mitochondria remain intact although they are usually smaller and fewer in number than those in adjacent, unaffected cells. Myofibrillar lysis can also be recognized by light microscopy as smaller, shrunken cells with a homogenous pale cytoplasm.

In the second type of myocyte damage, well-described in rabbit models (7), the cell undergoes vacuolar degeneration. The earliest manifestation is distension of the sarcoplasmic reticulum which eventually swells and coalesces to form large membrane-bound clear spaces in the cytoplasm (fig 4); this change can also occur with preservation of the mitochondria and nucleus.

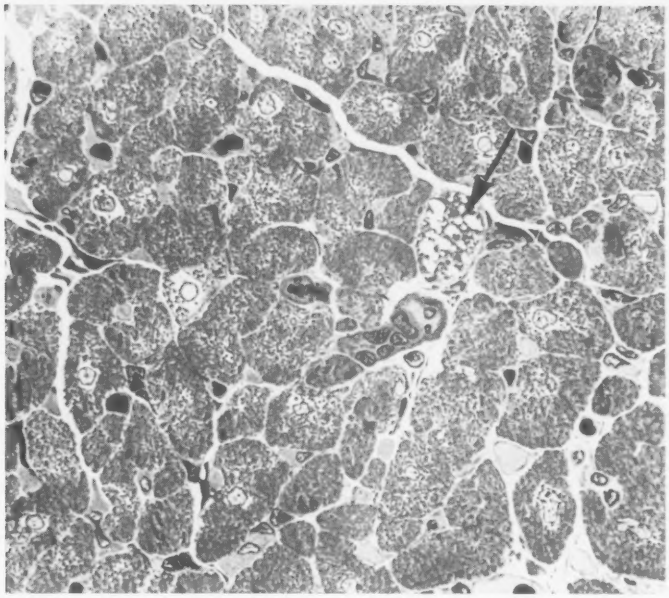

FIGURE 2.—Epon section demonstrating an isolated ADM-affected myocyte (arrow) adjacent to a capillary. Toluidine blue; original magnification, × 350.

These two types of degeneration may occur concomitantly in the same cell or in separate cells. These lesions eventually progress until the death of the myocyte at which time the mitochondria do degenerate by swelling and cristolysis, myelin figures appear, and the nuclei become pyknotic and disintegrate. In this study, the endothelial cells of the capillaries and small arterioles, as well as the nerve endings, were found to be unaffected when compared with normal control biopsies, even if they were from patients who had received maximal doses of anthracyclines. In addition, our data showed neither depletion nor increase in intramyocyte glycogen in severe, anthracycline-induced cardiotoxicity.

In order to make more meaningful clinicopathologic correlations and quantitative estimates, it was necessary to have a grading system for the biopsies. All of the biopsies were given a pathologic grade of 0–3 (table 3). A grade of 0 was given for normal morphology, a grade of 1 denoted very few cells affected with early changes of myofibrillar "drop-out" and early swelling of the sarcoplasmic reticulum, a grade of 2 was given when groups of cells were affected with loss of contractile elements and vacuolization of the sarcoplasm, and a grade of 3, the worst grade, was given to tissue which was diffusely affected by more severe changes including actual cell death. Fibrosis, although seen in ADM cardiotoxicity, was not used in the grading since it is a nonspecific finding and could have resulted from previous heart disease or mediastinal irradiation. Although severe cardiotoxic changes could be detected by conventional microscopy, 1-μ sections (epon-embedded) or electron microscopy was required to accurately grade the cellular damage. The grading system was modified to actual cell counts for some of the studies. This method involved counting all affected cells per unit area of tissue examined in 1-μ thick sections of at least ten blocks per biopsy.

Our data showed that anthracycline-associated myocardial degeneration occurred in virtually all patients treated with doses of 240 mg/m^2. The degree of morphologic cardiotoxicity is dose-related but influenced by many other factors including individual biologic variation. The lowest dose of anthracycline at which there was a morphologic change seen was 180 mg/m^2 and the highest dose associated with a normal biopsy was 400 mg/m^2. The lowest dose at which a pathologic grade of 3 was given was 272 mg/m^2; this was in a patient who had received previous cardiac irradiation. Additionally, it was found that the pathology grade corre-

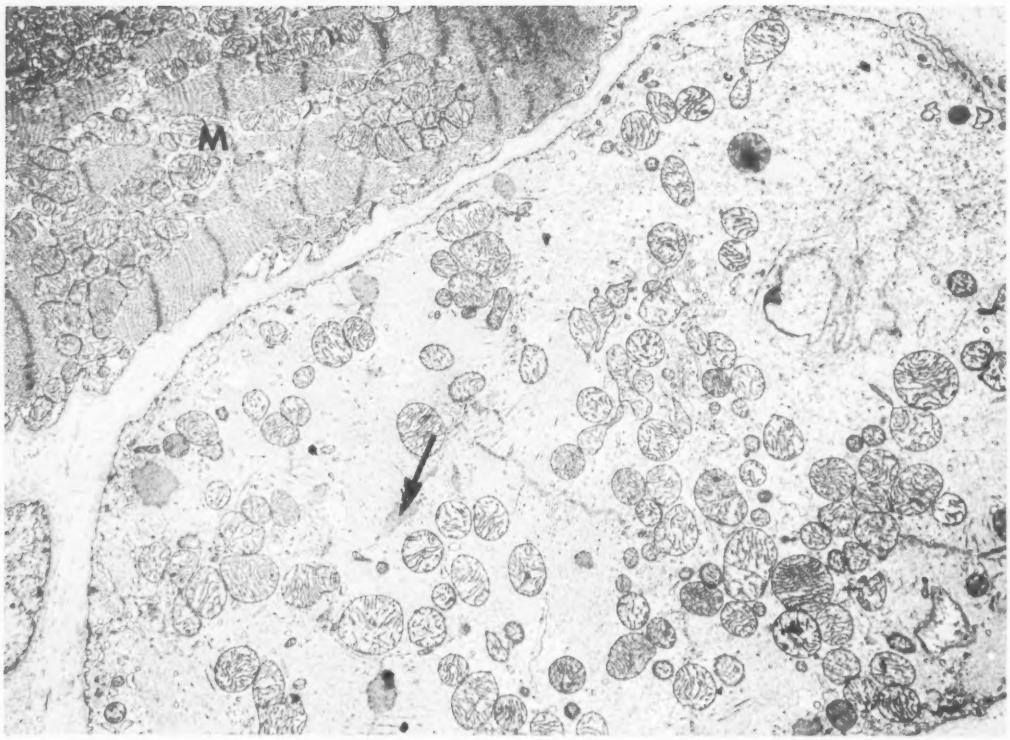

FIGURE 3.—Electron micrograph showing anthracycline-affected myocyte with myofibrillar loss and Z-band remnants (arrow) compared to adjacent unaffected myocyte (M). Original magnification, × 5750.

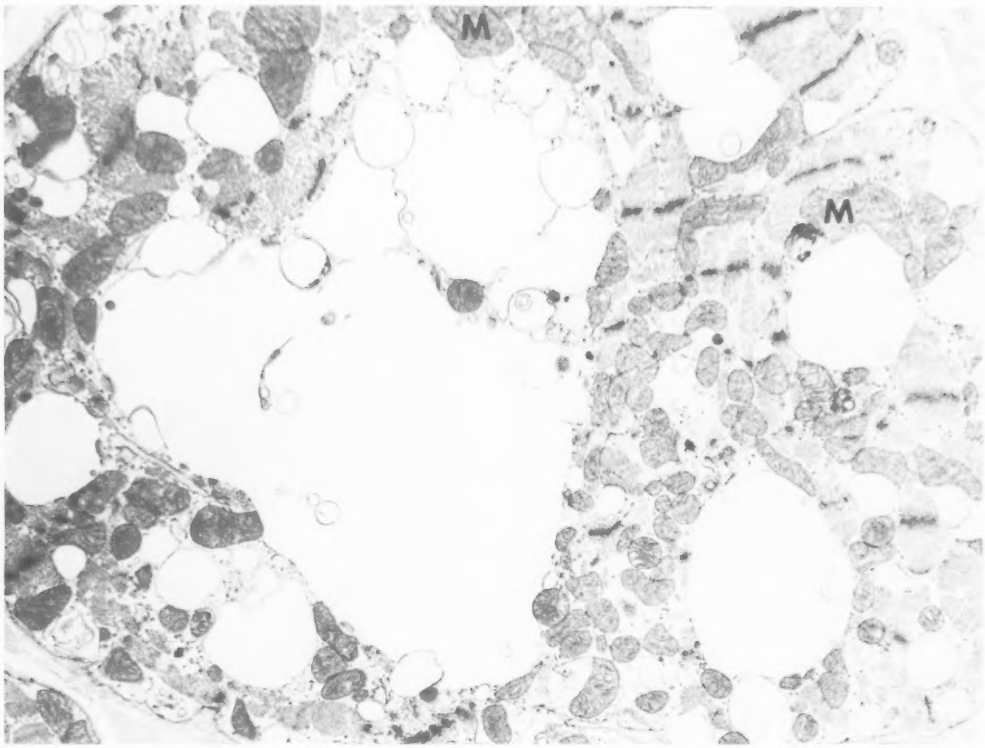

FIGURE 4.—Electron micrograph showing anthracycline-affected myocyte with vacuolar swelling of the sarcoplasmic reticulum (arrow). Note normal mitochondria (M). Original magnification, × 5750.

TABLE 1.—Endomyocardial biopsies in anthracycline-treated patients

Total biopsies	76 (60 patients)
Age range	19–78 yrs
Dose range	90–630 mg/m²
Last dose	3 wks to 2 yrs prior to biopsy
Serial biopsies	14 patients
Mediastinal radiation	12 patients (600–5700 rads)

lated well with heart failure: of seven patients identified by cardiac catheterization as having developed heart failure, five had grade 3 biopsies (the other two patients were > 70 years of age [one patient had mitral regurgitation], suggesting that their heart failure was due to causes other than anthracycline cardiotoxicity). The mean biopsy grades of the seven patients in heart failure (2.57 ± 0.30) were significantly higher ($P < 0.01$) than the biopsy grades of dose-matched controls (1.58 ± 0.19) not in heart failure.

Endomyocardial biopsies were examined in 12 patients receiving total doses of ADM from 90 to 445 mg/m². These patients had also received prior mediastinal irradiation from 600 to 5700 rads over periods varying from 6 months to 14 years prior to the biopsy (table 2). The severity of the pathologic grade in these 12 biopsies was compared with that of groups of dose-matched control patients who had not received mediastinal radiation (table 4). The results showed that the mean pathology grade of the group receiving irradiation (2.0 ± 0.89) was significantly higher ($P < 0.01$) than the grade of those not irradiated (1.18 ± 0.23). In addition, it was noticed that in nine of the 12 irradiated biopsies, the endothelial cells of capillaries and venules showed swelling and blebbing (fig 5), changes similar to those seen in acute irradiation (8) even though the irradiation was administered 6 months to 14 years previously. These studies lead us to conclude that previous radiation to the heart not only potentiates the danger of cardiotoxicity in man (9), but that ADM evokes a "recall" phenomenon of acute radiation change similar to that described in other tissues (10), even if the radiation was remote.

TABLE 3.—Pathologic grades of myocardial toxicity due to anthracyclines

Grade	Definition
0	No change from normal
1	Scanty cells with early change (early myofibrillar loss and/or distended sarcoplasmic reticulum)
2	Groups of cells with definite change (marked myofibrillar loss and/or cytoplasmic vacuolization)
3	Diffuse cell damage with marked change (total loss of contractile elements, loss of organelles, mitochondrial and nuclear degeneration)

In our studies we have also compared the pathologic changes of anthracycline cardiotoxicity in rabbits, mongrel dogs, and monkeys, and found that the cross species morphologic manifestations of cardiotoxicity is very similar to that seen in man. We have also had an opportunity to examine endomyocardial biopsies from patients treated with the anthracycline analogs, adria-DNA, daunorubicin, and rubidazone, and in all cases have found morphologic changes similar to those described above.

In conclusion, we feel that the endomyocardial biopsy does provide a useful means of monitoring anthracycline cardiotoxicity, and that it does serve as a useful tool for arriving at a rational process of dose limitation as well as providing reliable information on the identification of risk factors. We feel that it will be useful in monitoring clinical trials and animal studies of anthracycline analogs, pharmacologic antagonists, and different dose delivery schedules in the future.

TABLE 2.—Patients receiving mediastinal radiation and ADM

Patient No.	Age (yrs) /sex	Diagnosis	ADM (mg/m²)	Radiation (rads to apex)	Time elapsed (radiation to biopsy)
1	46/M	Lung carcinoma	395	< 600	8 mos
2	45/F	Lung carcinoma	430	< 600	1 yr, 5 mos
3	48/F	Hodgkin's disease	270	2940	2 yrs, 3 mos
4	48/F	Hodgkin's disease	373	2940	2 yrs, 8 mos
5	49/F	Histiocytic lymphoma	258	3000	7 mos
6	38/M	Hodgkin's disease	90	3500	3 yrs, 3 mos
7	35/M	Histiocytic lymphoma	270	4000	9 yrs, 3 mos
8	31/F	Histiocytic lymphoma	262	4510	6 mos
9	78/F	Breast carcinoma	445	4800	3 yrs, 6 mos
10	24/F	Hodgkin's disease	216	4900	6 yrs, 4 mos
11	66/F	Breast carcinoma	272	5000	14 yrs
12	24/F	Hodgkin's disease	330	5700	10 yrs, 6 mos

TABLE 4.—Effect of mediastinal radiation on the pathology grade of ADM-treated patients compared with unirradiated dose-matched controls (*from* ref 9)

	With radiation				Without radiation	
Patient No.	Dose rate (rads)	Heart failure	Pathology grade	ADM dose (mg/m^2)	Mean pathology grade (± 95% confidence limits)	Heart failure
6	3500	No	0	90 ± 60	—	
10	4900	No	1	216 ± 60	0.88 ± 0.54 (8 controls)	—
5	3000	No	2	258 ± 60	0.89 ± 0.46 (9 controls)	No
8	4510	No	1	262 ± 60	0.89 ± 0.46 (9 controls)	No
3	2940	No	2	270 ± 60	1.11 ± 0.46 (9 controls)	No
7	4000	No	1	270 ± 60	1.11 ± 0.46 (9 controls)	No
11	5000	No	3	272 ± 60	1.11 ± 0.46 (9 controls)	No
12	5700	Yes	3	330 ± 60	1.29 ± 0.70 (7 controls)	No
4	2940	No	3	373 ± 60	1.5 ± 0.63 (8 controls)	No
1	<600	Yes*	2	395 ± 60	1.38 ± 0.62 (8 controls)	No
2	<600	No	1	430 ± 60	1.38 ± 0.62 (8 controls)	No
9	4800	Yes	3	445 ± 60	1.43 ± 0.73 (7 controls)	Yes†
			Mean, 2.0 ± 0.89(SD)		Total mean, 1.18 ± 0.23(SD)	Yes†

*Intracardiac pressures were normal, but patient had cardiac dilation which later resolved.
†The same patient, who developed heart failure with a cumulative dose of 490 mg/m^2.

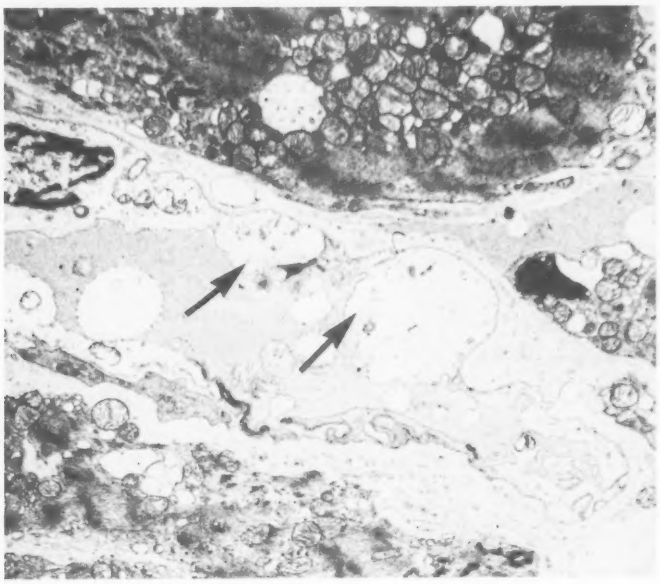

FIGURE 5.—Electron micrograph of a capillary with swollen endothelial cells (arrows) as seen in acute radiation change. This patient received mediastinal irradiation 10 yrs prior to ADM therapy which evoked this "recall" phenomenon. Original magnification, × 2875.

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Clinical Spectrum of Anthracycline Antibiotic Cardiotoxicity [1]

Michael R. Bristow,* Margaret E. Billingham, Jay W. Mason, and John R. Daniels [2]

SUMMARY

Anthracycline derivatives may produce early or late cardiotoxic reactions in man. Early effects include: (*a*) pericarditis-myocarditis which can affect patients with no previous history of cardiac disease and which carries a high mortality rate (~ 20%); (*b*) left ventricular dysfunction which may lead to clinically significant heart failure in patients with limited cardiac reserve; and (*c*) arrhythmias, the most common of which is sinus tachycardia. Symptomatic supraventricular tachycardia, heart block, and ventricular arrhythmias can occur, however, and may reflect primary effects on cardiac muscle or the conduction system. Late effects of anthracyclines are directly related to the degree of associated myocyte damage and include subclinical left ventricular dysfunction and overt heart failure. The implications for prognosis and further treatment are discussed for each of these entities and a common pathogenetic mechanism is proposed.

[Cancer Treat Rep 62:873–879, 1978]

The purpose of this paper is to review the various clinical presentations of anthracycline-associated cardiotoxicity. Data presented here are derived from studies performed in the last 3 years at Stanford University Hospital and from a review of the literature. Detailed analyses of the Stanford experience appear elsewhere (1,2).[3]

Anthracycline Cardiotoxic Reactions in Man

The cardiotoxic effects of anthracyclines in man are best divided into early and late effects (fig 1).

Early Effects

Early effects can be defined as cardiotoxic effects that can occur after one dose or course of drug and include a pericarditis-myocarditis syndrome, drug-induced left ventricular dysfunction, arrhythmias, and possibly myocardial infarction.

The pericarditis-myocarditis syndrome tends to affect patients with no previous history of cardiac disease. Pericarditis alone can occur, but three of five patients at Stanford with this syndrome have had significant myocardial dysfunction as well. One patient, whose clinical course was very similar to a previously reported case (3,4), died in cardiogenic shock. This was a 56-year-old woman who developed pericarditis 1 week after completing a 40-mg/m²/day × 4 course of daunorubicin as treatment for erythroleukemia. She died 20 days after her last dose of drug and autopsy findings showed a fibrinous pericarditis, epimyocarditis, and diffuse myocyte damage of the anthracycline type (fig 2). An electrocardiogram (ECG) taken on the day of this patient's death demonstrated an acute injury pattern in the inferior leads and a junctional rhythm; the patient ultimately died in ventricular fibrillation. No evidence of coronary artery disease or infarction was found at autopsy.

A right ventricular endomyocardial biopsy performed in a patient with clinical and catheterization evidence of pericarditis and myocardial disease is shown in figure 3. This patient, an 18-year-old girl with stem cell leukemia, developed pericarditis after receiving 180 mg/m² of daunorubicin over a 12-day period. Right and left heart catheterization and right ventricular biopsy were performed 27 days after her last dose of drug. Typical anthracycline

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Early effects
1. Pericarditis-myocarditis
2. Left ventricular dysfunction
3. Arrhythmias
4. Myocardial infarction (?)

Late effects
1. Subclinical left ventricular dysfunction
2. Overt heart failure

FIGURE 1.—Summary of anthracycline cardiotoxic effects in man.

changes are seen in the biopsy shown in figure 3 as well as fibrosis, presumably secondary to previous myocarditis and/or myocyte damage.

Another type of anthracycline-associated cardiotoxic effect that can occur after one dose of drug is left ventricular dysfunction with heart failure. Overt heart failure only affects patients with borderline cardiac reserve and is probably mediated by drug-induced transient left ventricular dysfunction described in noninvasive studies of the effects of adriamycin (ADM) in man (5,6). We have observed four patients over a 12-month period in whom administration of the first course of daunorubicin or ADM was associated with left heart failure. One of these patients, whose chest roentgenogram is shown in figure 4, developed pulmonary edema 12 hours after administration of 60 mg/m² of daunorubicin, with a total daunorubicin dose of 210 mg/m² given over 12 days. This patient suffered a myocardial infarction 8 hours later, which may have been precipitated by the increased workload placed on the heart by high left-sided filling pressures or by drug-induced coronary vasoconstriction (7). A case of myocardial infarction following administration of an anthracycline has previously been reported (8). Myocardial infarction or evidence of ischemia did not develop in the other three patients with heart failure, and all completely recovered and returned to their baseline cardiac status within days.

Arrhythmias were the first early effects of an-

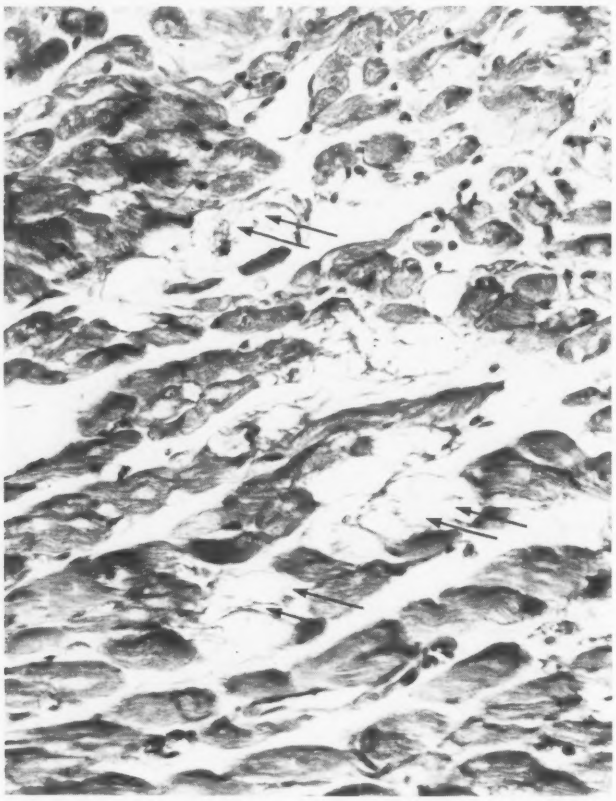

FIGURE 2.—Section of myocardium showing vacuolization of myocytes (arrow) in a patient who died in cardiogenic shock after receiving 160 mg/m² of daunorubicin over 4 days (*see* text for details) (Masson's trichrome, × 300).

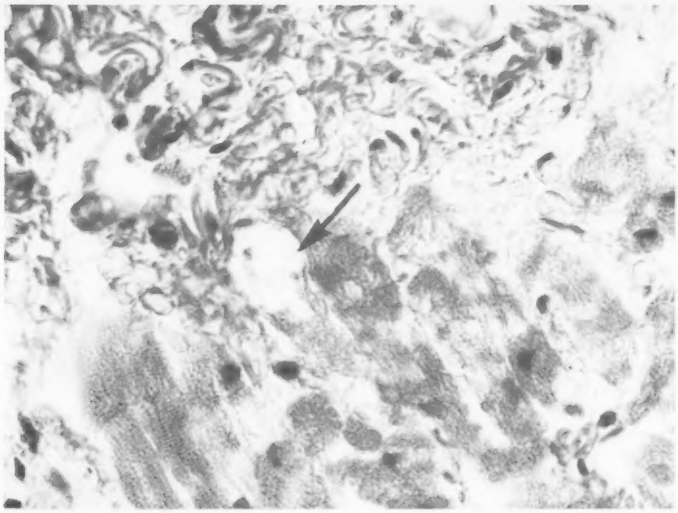

FIGURE 3.—Right ventricular endomyocardial biopsy, high power to show myocyte with typical anthracycline cytoplasmic vacuolization (arrow), in a patient who received 180 mg/m² of daunorubicin over 12 days (*see* text for details) (Masson's trichrome, × 500).

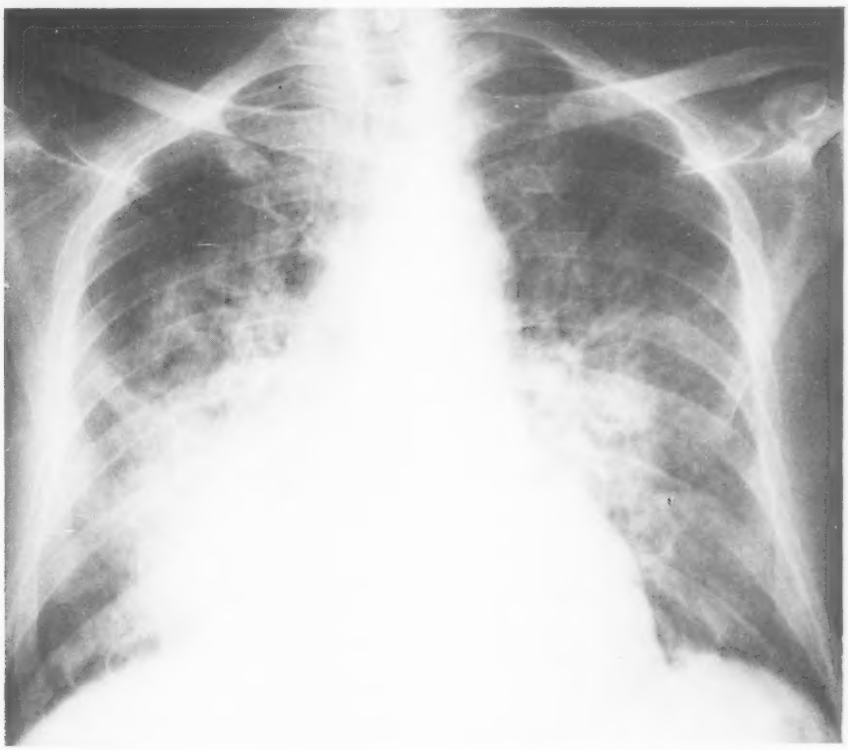

FIGURE 4.—Chest roentgenogram from an 81-yr-old man who developed pulmonary edema 12 hrs after receiving 60 mg/m² of daunorubicin, for a total of 210 mg/m² over 12 days (*see* text for details).

TABLE 1.—Comparison of biopsy score and PEP:LVET values between patients with overt heart failure and controls (matched for dose, mediastinal radiation, age, and length of time since last dose of drug)

	Heart failure	No heart failure (controls)	Student's t test statistic (*P* value)
No. of patients	9	9	—
Median dose (mg/m²)	445	430	—
Range	170–545	216–545	—
Mean dose (mg/m² ± SEM)	400 ± 44	401 ± 42	—
Mean biopsy score (± SEM)	2.67 ± 0.24	1.78 ± 0.28	2.44 ($P < 0.05$)
Mean PEP:LVET (± SEM)	0.49 ± 0.04	0.44 ± 0.03	0.44 ($P > 0.10$)

thracyclines to be recognized (9). Although electrophysiologic effects are usually not clinically important, the rhythm disturbances that occurred in the patient represented in figure 2 demonstrate that this is not always the case, as this patient suffered ventricular fibrillation just before her death. It was unclear from the histopathologic analysis if the rhythm disorder was due to inflammatory infiltrate or to anthracycline-induced damage to the specialized cells of the conduction system.

Late Effects

The cardiac effects of long-term administration of anthracyclines have been described extensively (2,9–16). Repetitive use of these agents is associated with dose-related myocyte damage (11) and heart failure (2,9). The heart failure is directly related to the amount of myocyte damage, as can be seen from table 1. These data compare the endomyocardial biopsy scores (0–3, with 0 = no, 1 = minimal, 2 = moderate, and 3 = severe damage) and pre-ejection period to left ventricular ejection time (PEP:LVET) ratios of nine patients with clinical and catheterization evidence of ADM-associated heart failure to those of dose-matched controls. There is a significantly greater amount of anthracycline-associated damage noted on biopsy in the heart failure group, most of whom had advanced changes.

An analysis of the first 33 ADM-treated patients studied at Stanford (2) revealed a dose-related increase in the amount of myocardial tissue damage as assessed by biopsy score. In contrast, the PEP:LVET ratio from these patients appeared to exhibit a threshold phenomenon and did not begin to increase until the higher dose ranges. Figure 5 presents an updated presentation of these data from an analysis of 68 biopsies performed on patients who had received ADM. These data are selected to exclude variables other than cumulative drug dose that could potentially influence the anthracycline cardiomyopathic process. Consequently, biopsies from 22 patients with previous mediastinal radiation (1,2), nine patients biopsied > 2 months after the last dose of drug (17), and two patients who received ADM at < 30 mg/m²/dose (18) are excluded, leaving 35 biopsies in 29 patients for which a meaningful dose-effect relationship could be analyzed. There were 32 PEP:LVET ratios obtained at the same time as the biopsies; PEP:LVET values for patients not biopsied are not included. Too few patients were biopsied at doses < 200 mg/m² to permit an analysis of data in this dose range. Figure 5 demonstrates that the degree of myocardial tissue damage from ADM administration is dose-related, but that the PEP:LVET values are not. The systolic time interval data shown in figure 5 again demonstrate a threshold effect, with prolongation at doses > 500 mg/m². The same phenomenon

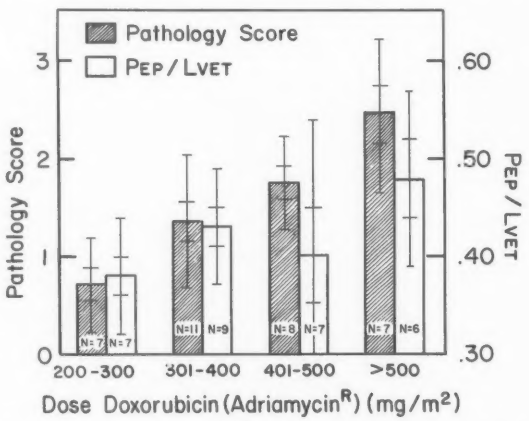

FIGURE 5.—Pathology score (left ordinate and shaded bar) and PEP:LVET ratio (right ordinate and open bar) vs cumulative dose of ADM: patients biopsied within 2 mos of their last dose of drug, no mediastinal radiation, and ADM schedule of at least 30 mg/m²/dose. Bars = SD and SEM.

is noted for catheterization abnormalities (19) and suggests that a certain amount of myocardial damage must occur before hemodynamic deterioration begins.

Several factors influence the anthracycline cardiomyopathic process or the associated heart failure. Previous mediastinal radiation potentiates the tissue damage (1,2) and the risk of developing heart failure is greater in patients > 70 years of age and patients with previous mediastinal radiation (2). The total cumulative dose of anthracycline should be substantially reduced if either of these risk factors is present, and a patient with both of them should probably not be treated with anthracyclines (2). Concurrent cyclophosphamide administration has been reported to increase the risk of developing heart failure in monkeys (20). Other investigators (5) have implicated cyclophosphamide as a risk factor for ADM cardiomyopathy in man, but we have not found this to be the case (2).

Anthracycline administration to a patient who has received previous cardiac radiation deserves further comment. The potentiating effects of radiation are dose-related in animals (21) and man (1) and therefore the dose of radiation received by the left ventricle is extremely important. More anthracycline can be administered if the previous radiation was confined to the base of the heart than if the apex of the left ventricle was in the treatment field. If there is a history of radiation-induced heart disease or evidence that the radiation dose to the heart was excessive, anthracyclines should not be administered. This is because, in addition to the potentiating effect of the previous radiation on the anthracycline process, drug administration may "recall" (1) the radiation effects. If this occurs, one is faced with acute and chronic radiation effects superimposed on the anthracycline changes, a situation that proves disastrous for the heart.

Any factor that reduces myocardial performance can be expected to reduce the total cumulative dose of anthracycline at which heart failure occurs, irrespective of the effect on the cardiomyopathic process. A patient with left ventricular dysfunction prior to the administration of anthracyclines will probably develop overt heart failure at doses less than empirical dose-limitation levels and should receive anthracyclines with caution. Whether anthracyclines can be safely administered in the presence of coronary artery disease is unknown, but information available at present suggests that, as long as left ventricular function is good and the coronary artery lesion is stable, the risk of precipitation of heart failure and/or myocardial infarction is slight.

Dose Limitation

Empirical dose limitation (22) has proven generally successful as a method for avoiding heart failure in patients receiving anthracyclines. However, this method breaks down in patients with significant early cardiotoxic manifestations, in patients with risk factors, and when there is a need to exceed standard dose-limitation levels.

Whether or not a patient who has had significant early cardiac effects from anthracyclines can receive more drug depends on the type of cardiotoxic effects encountered. Patients with the pericarditis-myocarditis syndrome can apparently receive further treatment[4] without developing a recurrent inflammatory process and, if absolutely essential and if left ventricular function permits, can receive more anthracycline. Patients who develop clinical evidence of heart failure after one dose of drug should probably not receive more anthracycline, as myocardial performance will only worsen as more myocyte damage is produced. We have not encountered patients in whom anthracyclines had to be discontinued because of drug-related arrhythmias, nor have we recommended stopping treatment because of exacerbation of pre-existing arrhythmias, but these are potential limitations to further anthracycline administration.

In the presence of risk factors (previous cardiac radiation and age ≥ 70 years), we lower the total cumulative dose substantially, to 300 mg/m^2, and exceed this only after hemodynamic and biopsy assessment of extent of cardiomyopathic change. These studies are also performed whenever there is a question of left ventricular dysfunction, whether from echocardiographic, systolic time interval, or clinical criteria.

Identification of the patients who can safely exceed empirical dose-limitation levels (450 mg/m^2 for ADM at our institution) is a particular challenge. As was seen in the early experience with ADM, not every patient who receives > 550 mg/m^2 develops heart failure. Patients appear to have significant individual variation in their susceptibility to anthracycline myocyte damage (2) and therefore to the development of heart failure. This point is made in figure 5, which shows relatively large variance of biopsy scores within each dose interval. As long as extensive morphologic damage (+3) has not occurred and good evidence (catheterization) is obtained that the degree of tissue damage is not impairing myocardial performance, more drug can be administered safely. We feel biopsy assessment of myocardial damage is necessary because of the

[4] *See* footnote 3.

1. Biopsy: no more anthracycline if advanced (+3) tissue damage
2. Catheterization: can receive more anthracycline if no abnormality of resting hemodynamics and biopsy $\leq +2$

When to study:

1. Any evidence of left ventricular dysfunction from clinical, echocardiographic, or phonocardiographic data
2. When patient needs to exceed standard dose limitation levels (Stanford criteria):
   a. ADM or daunorubicin alone or in combination: 450 mg/m^2
   b. Age $\geq$ 70 yrs: 300 mg/m^2
   c. Previous mediastinal radiation: 300 mg/m^2

FIGURE 6.—Dose limitation by morphologic and hemodynamic criteria.

near linear relationship of this test with dose and the positive correlation with overt heart failure (2) and catheterization abnormalities (19). The biopsy "score," therefore, should allow for some degree of prediction of (*a*) the myocyte damage that will be produced by further drug administration, and (*b*) whether that amount of cell damage will be associated with heart failure. Whether or not an individual patient's future biopsy score can be precisely predicted from a known dose-pathology score relationship is unknown and is under investigation by our group.

Careful hemodynamic assessment is also mandatory, as patients with limited cardiac reserve will develop heart failure with less tissue damage. Our dose-limitation studies are therefore designed to answer the questions, "How susceptible is this patient to anthracycline-associated myocyte damage?" and "How well is this patient's heart tolerating a given amount of tissue damage?" A general outline of this schema is given in figure 6. Validation of this approach is available by having administered ADM without incident to many patients who had abnormal systolic time intervals, had a reduction in ECG voltage, and had received the maximum recommended dose.

General Mechanism of Anthracycline Cardiotoxicity

The various cardiotoxic manifestations of anthracyclines can be explained by one underlying pathogenetic mechanism, drug-induced myocardial cell damage. The clinical presentation of this effect will depend on host factors, the type of heart cells involved, and the intensity and duration of insult. For example, pericarditis-myocarditis patients for whom tissue analysis is available show anthracycline-type cell damage and evidence of a recent or remote inflammatory process. Also, these patients usually have received large doses of anthracyclines over a short period of time. These observations suggest that an acute cell damage with a secondary inflammatory reaction is responsible for this syndrome. Arrhythmias can be explained by effects on the cells of the specialized conduction system. "Early" left ventricular dysfunction is probably the functional manifestation of the degenerative process that ultimately results in tissue damage, while "late" left ventricular dysfunction and heart failure are the results of this damage. Precipitation of myocardial infarction may be related to the left ventricular dysfunction, although it is possible that effects on the coronary circulation (7) play a role.

In summary, anthracycline antibiotics can produce a variety of cardiotoxic effects in man. It is likely that these various disorders are related to the same underlying pathologic process, but they should be considered individually in terms of their management and whether or not treatment should be continued.

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Noninvasive Profile in the Prospective Monitoring of Adriamycin Cardiomyopathy

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The cardiotoxic potential of adriamycin (ADM) is well known but remains incompletely defined (1–5). Both the electrical and contractile properties of the heart seem to be affected, although perhaps not by the same mechanism. Although dysrhythmia and electrophysiologic abnormalities have occurred (6), impairment of left ventricular performance is currently the most limiting factor during continued ADM therapy. Indeed, clinical congestive heart failure (CHF), occasionally resulting in death, has occurred during and following ADM therapy when continued to high dose levels.

Some correlation between the total dose of ADM and the development of heart failure exists. While the overall incidence of CHF with ADM therapy appears to be about 1%, a sharp increase in incidence is noted at higher dose levels. A 20% incidence is reported at total doses between 550 and 600 mg/m^2, while at doses > 600 mg/m^2, the incidence of CHF is reported to be 55% (6). However, cases of CHF have occurred at low doses of ADM, and some patients tolerate > 550 mg/m^2 without any functional impairment (4). Furthermore, certain other factors such as prior heart disease or mediastinal irradiation seem to accelerate the ADM cardiotoxic potential (4,6,7).

There is little information currently available about the spectrum of cardiac dysfunction in all patients receiving ADM. We sought to define the onset and progression of the ADM-associated cardiomyopathic effects. Using serial noninvasive parameters of cardiac function (systolic time intervals [STI], echocardiogram [Echo], chest roentgenogram, and electrocardiogram [ECG]), we hoped to outline the time-course of the impairment of left ventricular function. In addition, we hoped to learn which of these tests might be the most accurate in evaluating the development of cardiotoxicity. We also sought any clues which could allow more accurate prediction of which patients might be more susceptible to ADM cardiotoxicity.

This report represents preliminary data and tentative impressions drawn from this study currently in progress.

Part II (a separate study conducted by Drs. Leier and Weaver) is a retrospective analysis of the ECG changes seen in 49 patients receiving ADM when compared to 20 patients with similar malignancies not receiving ADM. Part II is presented separately in the last part of this report.

PATIENTS AND METHODS

Data from the first 24 patients in this study are presented; all patients had malignancy consistent with the use of ADM. Tumors included 13 carcinomas (six breast, three colon, two ovarian, one renal, and one endometrial), five non-Hodgkin's lymphomas, four sarcomas, and two hematologic tumors (one myeloma and one chronic myelocytic leukemia). Concurrent antineoplastic therapy included cyclophosphamide, vincristine, prednisone, 5-fluorouracil, DTIC, and methotrexate. No patient received digitalis or diuretics. Informed consent and excellent patient cooperation were obtained.

Data were collected from at least one baseline study prior to ADM therapy. Re-study of the noninvasive parameters was obtained 24 hours after the first ADM dose. On each subsequent dosing visit the noninvasive tests were repeated just prior to ADM injection. ADM was given on a 3-week schedule at dose levels from 20 to 65 mg/m^2/month. Time of followup varied from 3 to 11 months and included cumulative doses of 75–400 mg/m^2. There was no incidence of CHF or increasing cardiac symptoms in the entire group; hence, the study represents the noninvasive parameters of subclinical ADM cardiotoxicity.

STIs were recorded in compliance with methods previously described (8). The ratio of the pre-ejection period to the left ventricular ejection time (PEP/LVET) was evaluated. From the Echo, % Δ D was obtained in a method similar to that of Fortuin et al (9). Figure 1 displays a typical left ventricular Echo

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TABLE 1.—Change in PEP/LVET and %ΔD with respect to cumulative dose

Dose (mg/m²)	Change in PEP/LVET	N	± SEM	Change in %ΔD	N	± SEM
0–50	0.03	19	0.02	1.18	11	1.94
51–100	0.04	17	0.02	–4.70	10	1.17
101–150	0.03	14	0.02	–3.11	9	2.71
151–200	0.05	15	0.02	–3.50	8	1.40
201–250	0.09	11	0.02	–1.14	7	2.72
251–300	0.06	11	0.02	–4.00	8	2.67
301–350	0.08	8	0.02	0.00	4	3.98
351–400	0.03	7	0.02	–2.60	5	4.86

TABLE 2.—Change in PEP/LVET and %ΔD with respect to time

Time (mos)	Change in PEP/LVET	N	± SEM	Change in %ΔD	N	± SEM
24 hrs	0.00	19	0.02	0.85	13	2.60
1	0.03	21	0.02	0.36	11	1.90
2	0.05	18	0.02	–2.09	11	1.94
3	0.03	15	0.02	–4.40	10	1.51
4	0.05	15	0.02	–1.67	9	1.99
5	0.06	11	0.02	–3.78	9	2.39
6	0.02	8	0.02	–1.75	4	5.91
7	0.09	6	0.03	–9.50	4	3.40
8	0.04	8	0.03	–8.20	5	1.20
9	0.08	5	0.05	–2.50	4	2.47
10	0.06	5	0.03			
11	0.05	3	0.04			
12	0.12	1	—			

with the ventricular diameters outlined. Frontal heart areas were calculated from standard 6-foot posteroanterior teleroentgenograms according to the method of Meyer (10). ECG voltage was obtained by adding the total QRS deflections in I, AVF, V_5, and V_6 as obtained from a standardized 12-lead Marquette recording. This should correct for most changes of mean axis, including those patients whose axes change from a predominantly frontal to a horizontal orientation.

Since a clear baseline value was established for each parameter, all data were expressed as a change (Δ) from control. This was true of PEP/LVET, % Δ D, frontal heart area, or ECG voltage. Since our numbers remain small at this time, we did not apply tests of statistical significance (except in part II); however, standard error of the mean (SEM) is displayed where appropriate.

RESULTS

Data obtained from the serial noninvasive measurements of left ventricular performance in terms of time or cumulative dose are displayed in tables 1 and 2. Sample size (N) and SEM are also shown. The mean changes from control are shown in figures 2 and 3. A gradual and progressive reduction in these estimates of left ventricular performance is noted beginning at the first monthly interval. No change was noted at the first interval, 24 hours after the first dose. After the first six to eight observations, the N falls to very low numbers. Our study is currently active and most patients have not yet passed the seventh month of therapy.

Data from the change in heart area and ECG voltage are displayed in figures 4 and 5. No progressive change in heart area is noted. However, ECG voltage does show a progressive reduction with continued ADM therapy. This will also be discussed in part II.

No patient developed signs or symptoms of left ventricular dysfunction, and no significant dysrhythmia was encountered.

DISCUSSION

These data provide some information relative to the onset and time-course of the left ventricular functional impairment associated with ADM cardiotoxicity. The noninvasive estimates of ventricular

$$\%\Delta D = \frac{D(\text{diastole}) - D(\text{systole})}{D(\text{diastole})} \times 100$$

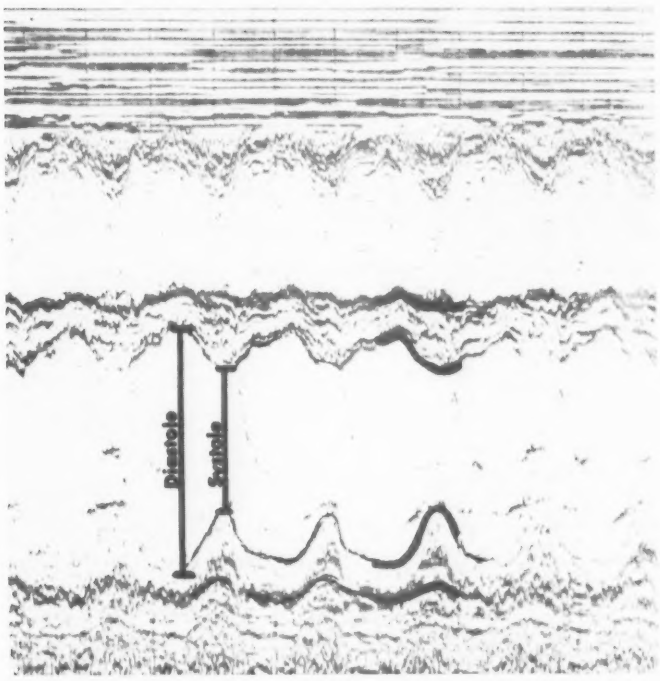

FIGURE 1.—Echo of left ventricular cavity. Systolic ventricular cavity. Systolic and diastolic diameters are outlined. Calculation of %Δ D is shown.

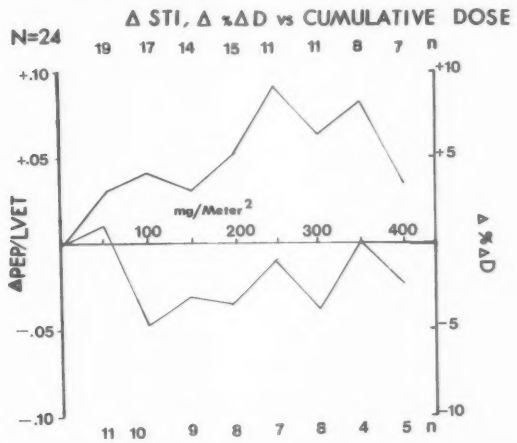

FIGURE 2.—Plot of change in PEP/LVET and %Δ D with respect to cumulative dose. Sample N and ± SEM are shown in table 1. Δ STI is shown above the dose axis; Δ D, below the axis.

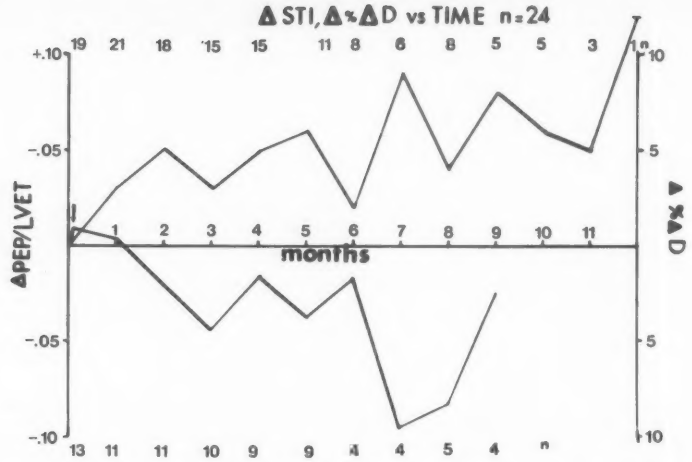

FIGURE 3.—Plot of change in PEP/LVET and % Δ D with respect to time. Sample N and ± SEM are shown in table 2. Δ STI is shown above the time axis; Δ D, below the axis.

performance (PEP/LVET, % Δ D) both show progressive changes with continued ADM therapy. Establishment of good baseline levels seems to be important since the values for "change from control" were more useful than the absolute numbers obtained from the STI or Echo. Since no patient as yet has developed any signs of impaired cardiac function, these data suggest that ADM cardiotoxicity begins early in the course of therapy and progresses (over the first few months) with continued treatment. Subtle changes in ventricular function may be detected by these techniques prior to the onset of clinical failure. Compensatory cardiovascular adjustments may also obscure the clinical signs of early ventricular impairment.

These data do not, as yet, suggest which noninvasive test is superior for monitoring ADM cardiotoxicity. The STI and Echo provide functional data while the ECG supplies information about electrical events (of which muscle mass is one determinant). While the Echo provides visual display of anatomic data, it is more difficult to obtain a suitable Echo than an adequate STI recording. For whatever reason, all three noninvasive tests (STI, Echo, and ECG) showed progressive changes with continued

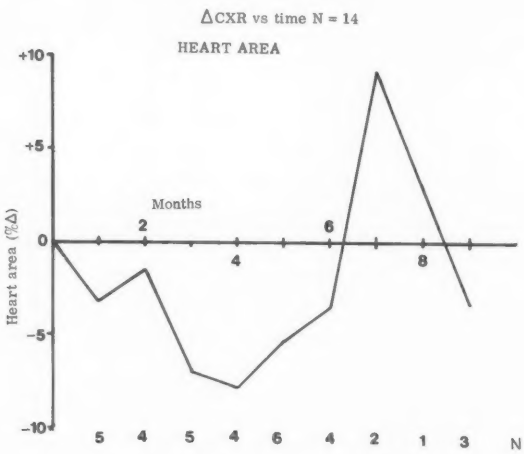

FIGURE 4.—Plot of heart area vs. time.

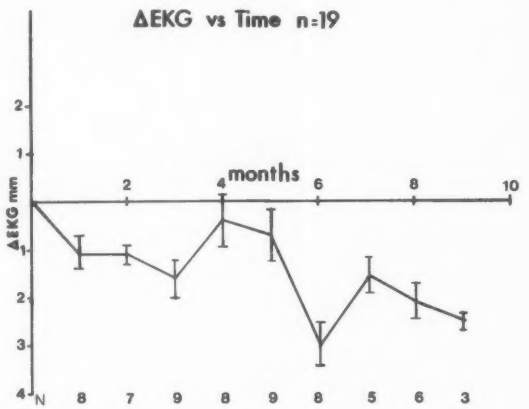

FIGURE 5.—Change of QRS amplitude vs. time. Brackets = ± SEM.

ADM therapy. Frontal heart area did not appear to be useful.

No information of predictive value was determined from our data. Small population size, short followup, and the complete absence of heart failure make predictive indices impossible as yet. Continued close followup of these patients and expansion of the study currently underway may yield better prognostic information. There does appear to be a continuing role for noninvasive monitoring of ADM cardiotoxicity.

PART II—RETROSPECTIVE ECG ANALYSIS

Serial ECGs of 49 patients receiving ADM were analyzed for the development of persistent changes. The ECG changes were compared with those of a control group of 20 patients receiving other chemotherapeutic drugs, which were comparable to the additional chemotherapy received by the ADM patients.

A minimum treatment period of 4 months was required for inclusion. Patients with known cardiac or pericardial disease, patients receiving daunorubicin or radiation therapy to the chest region, and patients with brain tumors were excluded.

A minimum of four scalar (12 lead) ECGs per patient were analyzed. The ECGs were performed at an average frequency of one every 2 months by a Marquette recording and amplification system (frequency response of DC to 120 hertz) at 25-mm/second paper speed.

Changes in amplitude, duration, and mean axis were evaluated for the p, QRS, and T waves in all 12 leads. An age- and sex-matched group of 20 patients with a variety of malignant neoplasms receiving comparable chemotherapeutic drugs and doses served as the control group.

ADM patients were grouped according to the amount of ADM received: group A, 0–250 mg/m^2; group B, 250–500 mg/m^2; and group C, > 500 mg/m^2. For each parameter of each ECG the difference (Δ) from baseline was determined; then, for each patient the sum of these differences was divided by the number of ECGs in that period. The data are thus expressed as Δ/ECG. These Δ/ECG values of each parameter for the control group and for each ADM subgroup were averaged and statistically analyzed with the Student's t test. Chi-square analysis was used for all parameters qualitatively assessed. (Complete data are now in press [ref 17]).

RESULTS AND DISCUSSION

The cardiotoxicity of ADM has focused attention on the cardiac assessment of patients receiving ADM. Various transient ECG changes have been reported (11–16) and generally occur in close proximity to the drug administration. Our analysis of serial ECGs of patients receiving ADM reveals few chronic changes at the various dose levels when compared to a control group. The P wave amplitude seems to decrease at ADM doses > 500 mg/m^2. In our series, atrial fibrillation occurred in 6% of the patients receiving ADM. Ventricular conduction defects (IVCDs or axis changes) occurred in both groups with similar frequency. The mean QRS voltage of the ADM-treated patients did not change significantly compared to controls (table 3), and did not differ between the ADM-treated patients who developed laboratory evidence of left ventricular dysfunction. Individual patients in both the control and ADM groups demonstrated episodic reduction in QRS voltage. The patients were not specifically evaluated for the occurrence of pleural and pericardial fluid and ascites during the period of reduced QRS voltage.

TABLE 3.—Effects of ADM on the QRS complex

ADM (mg/m^2, cumulative dose)	No. of patients	QRS complex amplitude Δ mm/ECG ($\bar{x}$ ± SEM)
Control	20	–2.0° ± 2.1
0–250	47	–1.5° ± 0.1
250–500	7	–1.4° ± 1.5
> 500	6	–1.2° ± 2.0

The ECG is frequently used in animal studies and in the clinic as the sole screening and diagnostic test to detect and follow the cardiotoxicity of ADM. This study indicates that the ECG alone is of limited value for this purpose.

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Adriamycin Cardiotoxicity: Early Detection by Systolic Time Interval and Possible Prevention by Coenzyme Q10

Engracio P. Cortes,[1,*] Mohinder Gupta,[1] Chia Chou,[1] V. C. Amin,[1] and Karl Folkers[2]

SUMMARY

Recent work suggests that adriamycin (ADM) cardiotoxicity results from the depletion of coenzyme Q10 (CoQ10) activity in myocardial mitochondria. CoQ10 is indispensable in the bioenergetics of coupled respiration of oxidative phosphorylation. It exists naturally in mitochondria, especially in the myocardium. Bertazzoli et al have reported a decrease in ADM-induced cardiotoxicity by CoQ10 both in vivo and in the in vitro isolated rabbit heart. The systolic time interval (STI) (pre-ejection period/left ventricular ejection time ratio) has been shown to increase (indicating cardiac dysfunction) with increasing doses of ADM. We have noted a gradual increase in the STI in eight of ten patients receiving 200–500 mg/m² of ADM. Two of these eight patients had congestive heart failure (CHF) at doses of 200 and 350 mg/m². The continued daily oral administration of 50 mg of CoQ10 beginning with the first dose of ADM resulted in a decreased incidence of cardiac dysfunction, and a gradual increase in STI occurred in only two of eight patients receiving 200–400 mg/m² of ADM. CHF was observed in one patient at a dose of 350 mg/m². It is suggested that CoQ10 may benefit the cardiac function in ADM-treated patients. CoQ10 was nontoxic and did not affect the antitumor activity or modify the ADM-induced bone marrow toxicity. A prospective randomized study comparing ADM with and without CoQ10 is in progress.

[Cancer Treat Rep 62:887–891, 1978]

Although a variety of mechanisms have been postulated as being responsible for or contributing to the dose-dependent cardiotoxicity of adriamycin (ADM) (1), none of the postulates is convincing enough to be universally accepted. One mechanism being considered is the potent inhibition of ADM on coenzyme Q (CoQ10) in the heart mitochondria (2). CoQ10 is indispensable in the bioenergetics of coupled respiration of oxidation phosphorylation (3). It exists naturally in the mitochondria of the heart.

Gosalvez et al (4) reported that ADM inhibits mitochondrial respiration by nearly 100% at a 1-mm concentration. On electron microscopy of ADM-induced cardiotoxicity, there was Z-line irregularity, degeneration of myofibrils, enlargement and irregularity of mitochondria containing disorganized cristae, and prominent electron dense bodies (5).

Preliminary studies of Bertazzoli et al have shown that CoQ10 has an antagonistic effect on the ADM-induced cardiotoxicity in isolated (6), as well as in vivo (7), rabbit heart. Similarly, Zbinden et al (8) have shown that rats receiving equivalent doses of CoQ10 did not develop electrocardiographic (ECG) changes indicating a protective action of the enzyme against ADM cardiotoxicity.

In man, several ECG abnormalities may result from ADM administration which may not be dose-related (9). Several noninvasive techniques such as the measurement of systolic time intervals (STI) (10) and echocardiogram (11) had been utilized to detect presymptomatic ADM-induced cardiotoxicity.

The objectives of the present study are to determine the usefulness of STI in detecting cardiac dysfunction during the course of ADM therapy and to determine the protective effect of CoQ10 on

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ventricular function of patients receiving ADM as measured by serial STIs.

MATERIALS AND METHODS

Ventricular function was measured by means of STI (ratio of pre-ejection period to left ventricular ejection time) (PEP/LVET) before and every 2 weeks after each course of ADM. The STI was measured by simultaneous recordings of ECG, phonocardiogram, and carotid pulse tracing at a paper speed of 100 mm/second using multichannel photographic system (Electronics for Medicine). Recordings were made in the postabsorptive state between 9:30 AM and 11:00 AM. The LVET, PEP, and QS2 (total electromechanical systole measured from the onset of the QRS complex of ECG to the first high-frequency vibration of the second heart sound) were corrected for heart rate by regression equations reported previously by Weissler et al (12).

Ninety-three consecutive patients with histologically proved advanced carcinoma were entered in the study. None had prior history of heart disease and none had abnormal ECG prior to ADM therapy. Chemotherapy consisted of vincristine (1.4 mg/m^2), ADM (50 mg/m^2), and cyclophosphamide (500 mg/m^2) (VAC) given iv at 4-week intervals. Most of the patients had bronchogenic carcinoma treated previously with radiotherapy.

The study was done in two stages:

Stage I.—Determination was made of serial STIs in 63 patients treated with VAC alone from January 1975 to June 1976. Only ten of 63 patients were evaluable for ADM cardiotoxicity (a minimum followup of 5 months and a total ADM dose of $\geq$ 200 mg/m^2). Although some of these patients were given either daily digoxin or prednisone at the start of VAC therapy, neither of these two drugs seems to have any influence on the serial STI values compared to VAC alone.

Stage II.—Determination was made of serial STIs in 30 patients treated with CoQ10 and VAC from July 1976 to June 1977. CoQ10 (10-mg tablets) was given at a dose of 50 mg/day orally at the start of the first course of VAC therapy. Only eight of 30 patients were followed for $\geq$ 5 months and had total ADM doses of $\geq$ 200 mg/m^2.

RESULTS

The clinical characteristics of patients treated with VAC alone (stage I study) and VAC plus CoQ10 (stage II study) are shown in table 1. The pretreatment characteristics between the two groups were comparable except that patients in the ADM plus CoQ10 group were older.

TABLE 1.—Characteristics of patients treated with > 200 mg/m^2 of ADM alone and ADM + CoQ10

Characteristic	ADM	ADM + CoQ10
No. of patients	10	8
Men	7	4
Women	3	4
Age (mean ± SE)	49.4 ± 0.38	66.2 ± 2.7
Heart rate (mean ± SE)	92 ± 14	92.5 ± 21
PEP/LVET (mean ± SE)	0.348 ± 0.02	0.360 ± 0.01
No. of patients with—		
Bronchogenic carcinoma	8	6
Other carcinoma	2	2
Prior radiation	6	5

STI in ADM-Alone Group

Eight of ten patients showed a gradual prolongation of STI with increasing doses of ADM. Two of these eight patients had congestive heart failure (CHF) at STI values of 0.50 and 0.45 (normal, 0.34 ± 0.04) after 200 and 350 mg/m^2 of ADM respectively (fig 1). Both patients had prior chest irradiation, daily digoxin at the start of ADM, and improvement of STI with diuretic therapy.

The serial STIs (mean) in ten patients receiving VAC alone gradually increased with increasing doses of ADM (fig 2).

STI in CoQ10 and ADM Group

The continued daily oral CoQ10 administration at the start of VAC resulted in a gradual increase of STI in only two of eight patients with increasing doses of ADM. CHF was observed in only one patient with an STI of 0.42 after 350 mg/m^2 of ADM (fig 3). She was previously treated with chest irradiation.

The serial STIs (mean) in eight patients receiving VAC and CoQ10 gradually improved or shortened with increasing doses of ADM (fig 4).

STI in Patients With Progressive Disease

None of the 75 patients whose disease progressed after three courses of VAC therapy (< 200 mg/m^2 of ADM) developed CHF attributable to ADM. Most of these patients, however, developed an STI prolongation with or without CoQ10, as did some patients treated with forms of chemotherapy other than ADM (fig 5).

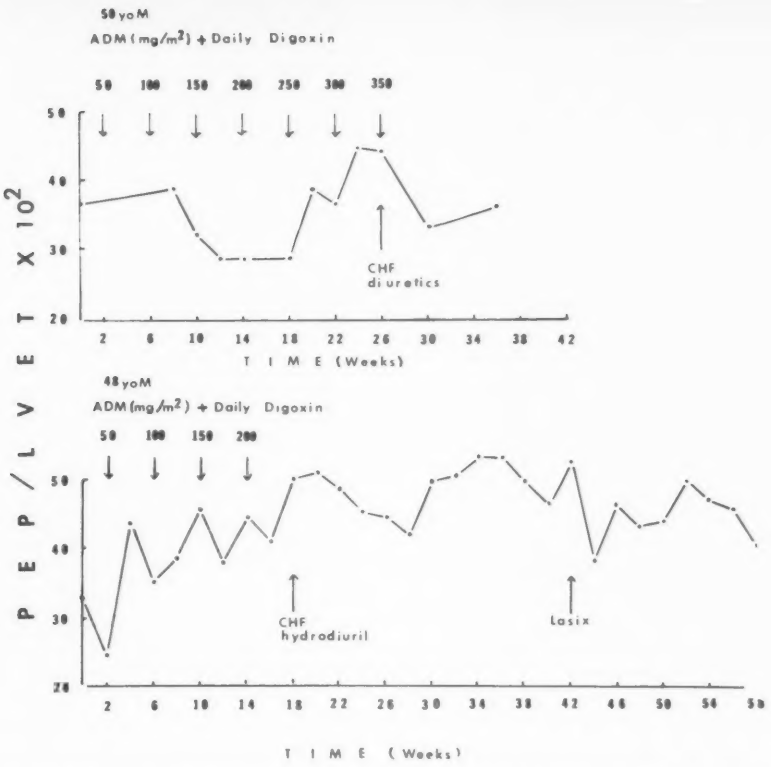

FIGURE 1.—Serial STI of 2 patients who developed ADM-induced CHF. PEP/LVET was multiplied by 10^2 to obtain whole Nos.

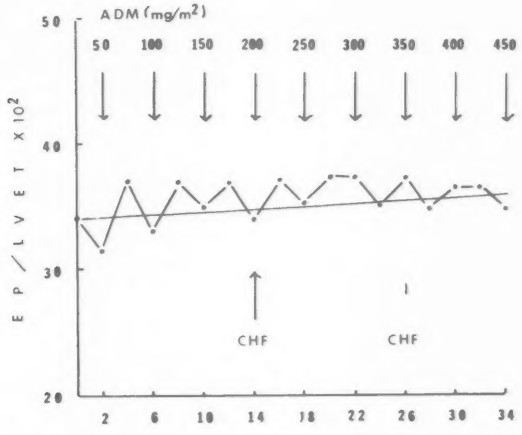

FIGURE 2.—Serial STI (mean) in 10 patients receiving VAC therapy alone.

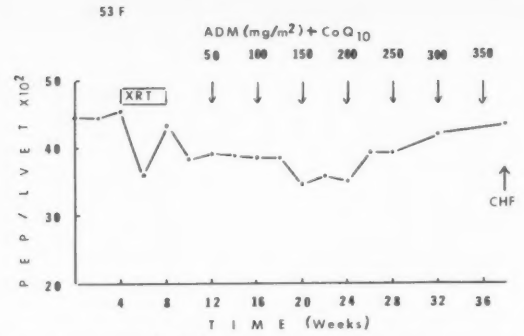

FIGURE 3.—Serial STI of a patient with bilateral adenocarcinoma of the lung before and after chest irradiation and during the course of ADM + CoQ10 therapy.

DISCUSSION

The present study confirms the previously reported prolongation of STI with increasing doses of ADM (10). Our study also shows that STI values tend to be intermittent (rise and fall) and sometimes erratic making it difficult to interpret one or two STI values during ADM therapy.

Although the ADM-induced CHF in three patients correlates well with the prolonged STI levels, there were other patients in the study with similar or higher STI values who did not manifest overt CHF. The occurrence of heart failure, therefore,

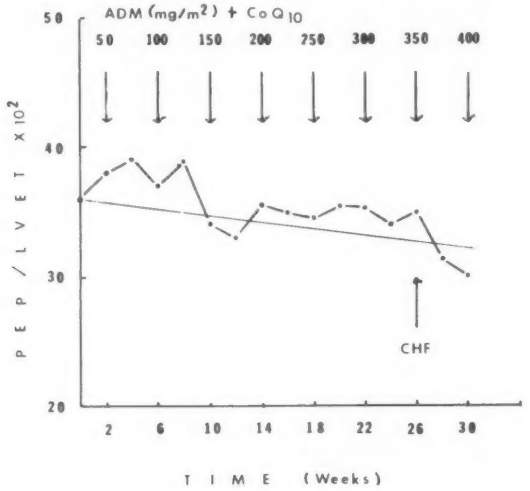

FIGURE 4.—Serial STI (mean) in 8 patients receiving ADM + CoQ10.

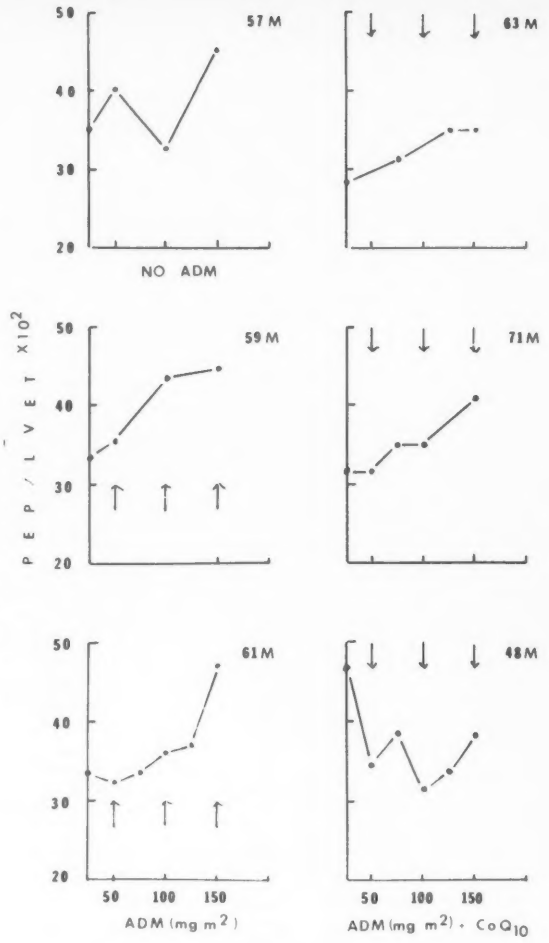

FIGURE 5.—Serial STI of patients with progressive lung cancer. Uppermost left = no ADM; middle and lowermost left = ADM alone; right column = ADM + CoQ10.

could not be predicted by STI levels despite serial determinations, and decisions as to when to stop or continue ADM therapy before the maximum recommended dose is reached could not be made. The STI determination, however, is sensitive enough to detect early ADM-induced ventricular dysfunction, and can be useful only if correlated with good clinical examination.

The well-known high level of mitochondria in cardiac tissue and the concomitant high concentration of CoQ10 in such mitochondria gave credence to the concept that CoQ10 inhibition is the result of ADM-induced cardiotoxicity. The preliminary data

of CoQ10 antagonizing the cardiotoxic effect of ADM both in in vitro and in vivo studies strengthen the above concept. The data of the present series suggest that daily administration of CoQ10 may benefit the cardiac function (shortening or improvement of serial STI) during ADM therapy. CoQ10 was nontoxic and did not affect the antitumor activity or modify the ADM-induced bone marrow toxicity.

The group of patients who had progression of their disease demonstrated an increasing STI with or without ADM (< 200 mg/m^2) and with or without CoQ10. These ventricular dysfunctions may be the result of metabolic abnormalities from cancer itself or from cor pulmonale produced by increasing pulmonary lesion.

The preliminary data showing the protective action of CoQ10 in developing ADM-induced cardiotoxicity are provocative and need to be confirmed. A prospective randomized study is ongoing in patients with tumor types highly responsive to ADM to allow a longer followup of their cardiac function with or without CoQ10.

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Systolic Time Intervals in Monitoring Adriamycin-Induced Cardiotoxicity [1]

Stanley P. Balcerzak,* John Christakis, Richard P. Lewis, Harry M. Olson, and Louis Malspeis [2]

SUMMARY

Left ventricular function of 48 patients treated with adriamycin (ADM) was assessed serially with systolic time intervals (STI). Twenty-one patients (group I) showed no significant increase of the ratio of the pre-ejection period (PEP) to the left ventricular ejection time (LVET). Nine patients (group II) had a significant but transient worsening of the ratio. Eighteen patients (group III) had a significant and persistent or progressive increase of the PEP:LVET ratio. The mean cumulative ADM dose was not statistically different between these three groups, but all nine patients who developed heart failure were in group III. All patients had abnormal PEP:LVET ratios at the time of failure. Seven of the nine patients with failure received digitalis and six responded. Six of the 18 patients in group III had prior mediastinal irradiation, whereas none of the patients in groups I and II had received such therapy. Mean baseline PEP:LVET ratios were higher in groups II and III than in group I and four of the nine patients who developed failure had abnormal baseline ratios. The three groups were similar in other respects such as incidence of pre-existing heart disease by history, age, tumor type, and cyclophosphamide therapy. Because heart failure was more frequent and milder in the present study than in previous reports, routine use of STI may alert the physician to the early occurrence of myocardial injury. The development of abnormal STI per se, however, need not require termination of ADM therapy as was indicated by our experience with group II.

[Cancer Treat Rep 62:893–899, 1978]

Because systolic time intervals (STI) are a sensitive indicator of left ventricular function and are frequently abnormal in patients treated with adriamycin (ADM) (56%), they should prove useful in elucidating factors responsible for variation in the susceptibility of patients to ADM-induced cardiomyopathy. For example, correlation of cardiac function measured by STI with pharmacokinetics and tissue uptake of ADM should be possible. Preliminary studies in rats with ^{14}C-labeled ADM possessing high specific activity (24.6 millicuries/mmol) suggest that uptake and disappearance of radioactivity in the heart are comparable to uptake and disappearance in other tissues. Whether patients who develop abnormal STI will be shown to handle this radiolabeled drug differently than those whose STI remain normal requires further study.

Cardiotoxicity limits the therapeutic effectiveness of the anthracycline drugs, ADM and daunorubicin (1,2). The severity of cardiac damage relates in part to the cumulative dose of each drug. The incidence of heart failure with daunorubicin is 1.5% at a total dose of 600 mg/m^2 and 12% at a dose of 1000 mg/m^2 (2). With ADM, the incidence of heart failure is reportedly infrequent at total doses < 550 mg/m^2 (0.27%), but is much more likely to occur at doses above that level (30%) (1).

The cardiac injury induced by the anthracyclines appears to occur early and to progress with additional drug exposure rather than to develop abruptly after a certain total drug dose has been

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reached. Endomyocardial biopsies show increasing abnormalities on light and electron microscopy with increasing total ADM dose (3). STI also frequently become progressively abnormal at total doses of ADM > 300–400 mg/m^2 (3,4). Neither morphologic nor STI abnormalities, however, show a close linear correlation to cumulative dose (3). This variability in degree of cardiac damage for a given total dose of anthracycline is also reflected in the occasional occurrence of cardiac failure at doses < 550 mg/m^2 for ADM or 1000 mg/m^2 for daunorubicin (2,4), and in the significant number of patients treated with cumulative doses over these limits without the onset of heart failure.

The present study expands upon an earlier report in which data were reported suggesting the usefulness of STI in monitoring ADM-induced cardiomyopathy. This larger study shows that STI are sensitive to cardiac damage caused by ADM and that they may be used to characterize a group of patients with the increased likelihood of developing heart failure.

MATERIALS AND METHODS

Studies in Man

Records of patients who had received ADM between 1972 and 1975 at Ohio State University were examined. Forty-eight patients who met the criteria listed below formed the population for this study. The criteria were:

(1) measurement of STI before initiation of therapy and within 3–6 weeks after therapy;
(2) a total of at least three serial STI measurements and a followup of at least 3 months;
(3) no evidence of invasion of the heart or the pericardium by the tumor before ADM treatment;
(4) no alteration in digitalis therapy if the patient had been receiving it prior to ADM administration. (If such treatment were initiated during chemotherapy, the patient was evaluated up to this point. Response to digitalis was evaluated separately.)

All patients received ADM in doses ranging from 40 to 75 mg/m^2 as a single bolus injection every 3–4 weeks alone or in combination with other agents on treatment protocols used by the Southwest Oncology Group.

STI were measured as described by Weissler (5). The ratio of the pre-ejection period (PEP) to the left ventricular ejection time (LVET) was used to express STI. PEP is the interval from onset of ventricular depolarization to the beginning of ventricular ejection. LVET is the phase of systole during which the left ventricle ejects into the arterial system and is the interval between the beginning of the upstroke of the carotid arterial pulse and beginning of the second heart sound. The normal mean value for the PEP:LVET is 0.34 ± 0.04 SD. Increases in PEP:LVET to ≥ 0.42 indicate diminished left ventricular performance.

Patients who received ADM were classified according to the pattern of STI. Group I included those patients who showed no significant increase in the PEP:LVET ratio during therapy; 21 of the 48 patients were in this group. Group II included nine patients who had a significant but only transient worsening of the ratio. Group III included 18 patients who had a significant and persistent or progressive increase of the ratio. The increase in the PEP:LVET ratio was considered significant if the difference from the baseline was ≥ 0.07 and the absolute value of the ratio was > 0.42 which is two SDs above the normal mean. In cases in which the baseline value was abnormal, an increase of 0.05 was considered significant.

Animal Studies

Plasma disappearance and tissue uptake of ADM were investigated using ADM labeled with ^{14}C in the 14th position. This radiolabeled drug was prepared by a technique previously described and which uses ^{14}C-Diazold as the source of the label (6). Specific activity of the labeled compound was 24.6 millicuries/mmol.

Fifteen New Zealand black rats, 40 days old and weighing 60–80 g each, were injected iv with radiolabeled ADM at a dose of 1 mg/kg. Rats were exsanguinated under light ether anesthesia in groups of three at 0.5, 1, 6, 12, and 24 hours after injection. Tissues were blotted free of blood and frozen immediately for later measurement of radioactivity after oxidation (Packard 303 Sample Oxidizer) of a portion of each sample.

RESULTS

A comparison of the total cumulative dose and the rate of administration of ADM among the three groups of patients is shown in figure 1. Although the rate of administration was higher in group III as compared to the other two groups, the difference was not statistically significant. Mean cumulative doses also were not different among the three groups. In addition, no significant differences were found in age, sex, and tumor type among the three groups.

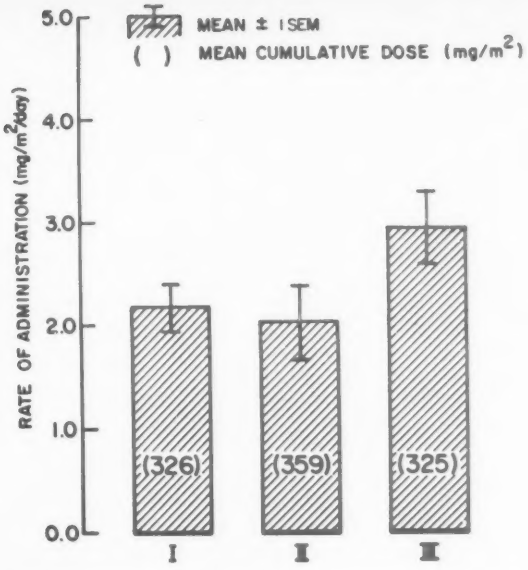

FIGURE 1.—Rate of administration and mean cumulative dose of ADM in groups I–III. Patients in group I were those with no significant change in PEP:LVET ratios. Group II included those with only a transient increase in ratios. Group III included those with a significant and persistent or progressive increase in ratios.

Figure 2 depicts the change in STI with therapy. As expected by definition, mean ratios after therapy in group III and upon transient worsening in group II were significantly higher than ratios before therapy in each of these groups. Mean baseline ratios in groups II and III, although within the normal range, were significantly higher when compared to the baseline mean of group I.

The frequency of heart failure in each group and possible risk factors which may be associated with its development are shown in table 1. No patient in groups I and II developed heart failure during therapy or up to 8 months afterward. In striking contrast, however, nine of 18 patients in group III developed clinical symptoms and findings of congestive heart failure. This occurred 2 days to 6 weeks after the last ADM injection. Diagnosis of heart failure was made by house staff, fellows, or attending physicians independently of the investigators of this study.

Table 1 also shows that the incidences of previous heart disease and concurrent cyclophosphamide therapy were not different in the three groups. The incidence of prior irradiation to the mediastinum, however, was significantly higher in group III compared to the other two groups. Six of the 18 patients in group III had received radiation therapy to the

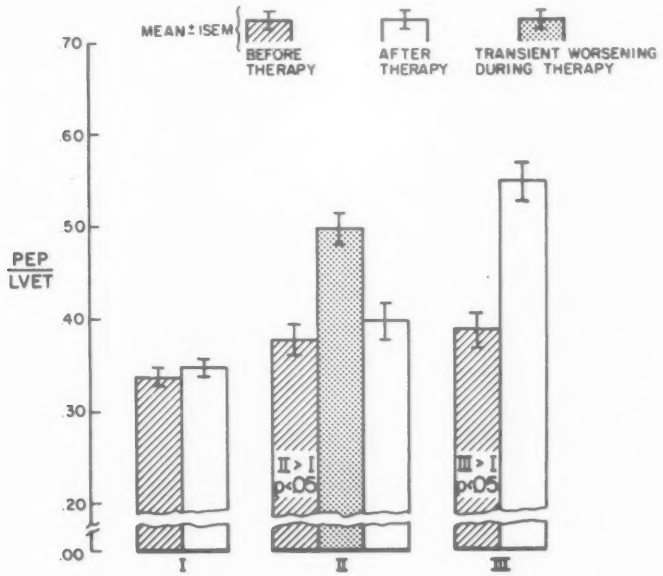

FIGURE 2.—STI in patients receiving ADM therapy.

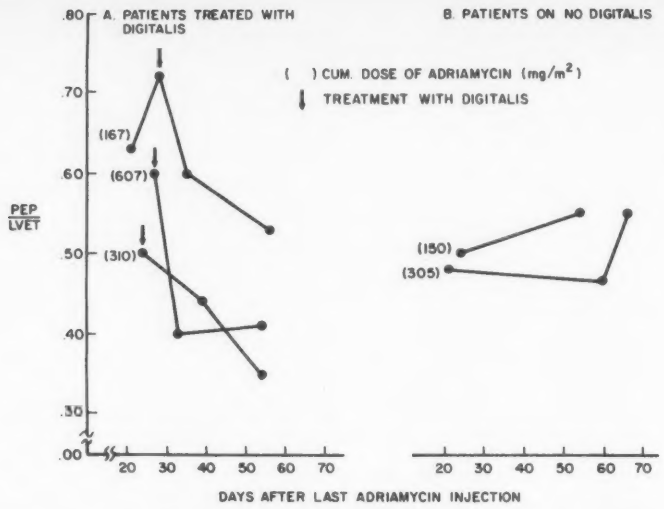

FIGURE 3.—Effect of digitalis on left ventricular function in patients having received ADM.

mediastinum and two (patients 1 and 8, table 2) of these six developed heart failure.

Table 2 shows the STI and the dose of ADM in the nine patients who developed heart failure. Abnormal PEP:LVET ratios preceded the appearance of heart failure in seven of eight patients who had STI measured within 2 months before the onset of failure. Ratios were abnormal in all patients at the time of heart failure. Six of the nine patients had received total cumulative doses < 550 mg/m² and two had received very low doses. One of these two patients had prior mediastinal irradiation. None of

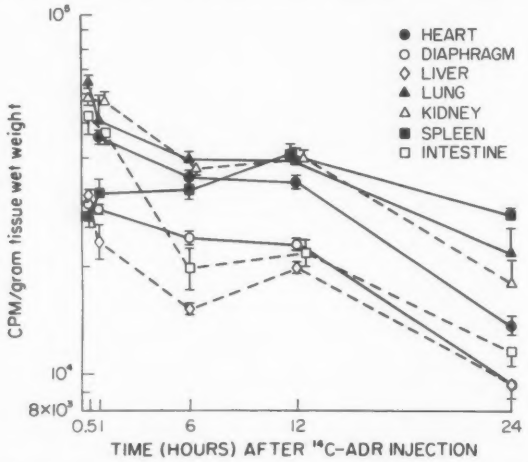

FIGURE 4.—Radioactivity of ¹⁴C-ADM in tissues of rats. Results are expressed as cpm/g of tissue wet weight.

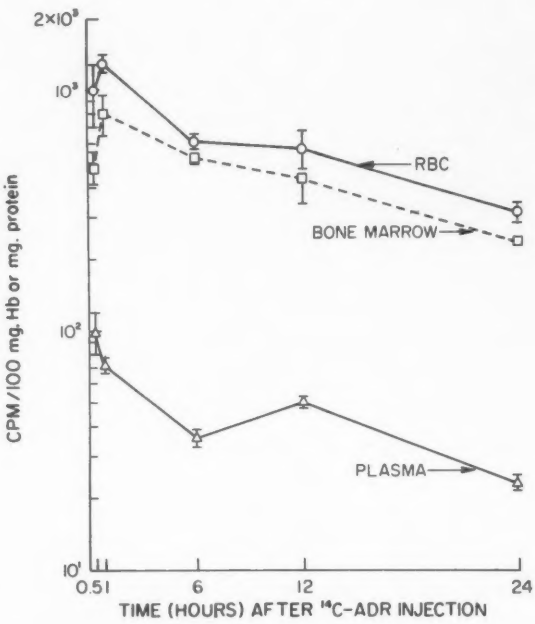

FIGURE 5.—Radioactivity of ¹⁴C-ADM in plasma, red cells, and bone marrow of rats. Red cell radioactivity is expressed as cpm/100 mg of hemoglobin; plasma and marrow radioactivity is expressed as cpm/mg of protein. These data indicate that radioactivity in blood contributed little to tissue counts. For example, at 12 hrs, 1 ml of whole blood may be calculated to contain 2350 cpm, whereas radioactivity in the spleen is 42,000 cpm/g.

TABLE 1.—Possible risk factors in development of congestive heart failure

Group	Total No. of patients	No. of patients with— Previous heart disease*	Concurrent cyclophosphamide*	Prior mediastinal irradiation	ADM-induced congestive heart failure
I	21	3	9	0	0
II	9	2	2	0	0
III	18	4	5	6†	9‡

*No statistically significant differences among the 3 groups.
†Frequency in group III > I ($P < 0.01$).
‡Frequency in group III > I ($P < 0.01$) and II ($P < 0.05$).

TABLE 2.—STI and ADM dose in patients with congestive heart failure

Patient No.	PEP:LVET 3–8 wks prior to congestive heart failure	Total dose of ADM (mg/m²)	PEP:LVET at time of congestive heart failure
1	0.39	152	0.48*
2	0.51*	167	0.63*
3	Not determined	235	0.53*
4	0.59*	350	0.76*
5	0.52*	402	0.65*
6	0.45*	425	0.49*
7	0.46*	551	0.57*
8	0.47*	607	0.60*
9	0.48*	674	0.70*

*Abnormal PEP:LVET.

these nine patients had a history of previous heart disease and only one had hypertension, but four (patients 2, 3, 7, and 9) had abnormal baseline ratios.

Heart failure was usually modest and in only one instance was it severe. No patient developed fatal heart failure. Seven of the nine patients were treated with digitalis and six responded both clinically and by a significant decrease of the PEP:LVET ratio. Representative responses to digitalis are shown in figure 3. Figure 3A shows results in those who received digitalis. As can be seen, response, when it occurred, was prompt. As shown in figure 3B, ratios remained high or increased further in the two patients who did not receive digitalis.

The activity of ^{14}C-ADM in tissues of rats is shown in figure 4. The concentration of radioactivity in ventricular myocardium was similar to that in other tissues examined although the mean activity in the heart was consistently greater than in the skeletal muscle (diaphragm). The kinetic pattern of radioactivity for the 24 hours of observation was also similar for all tissues with the exception of the spleen. As shown in figure 5, ^{14}C radioactivity also fell promptly in red cells, plasma, and marrow.

DISCUSSION

Sensitivity to ADM cardiotoxicity varies considerably. In the present study, 44% of patients (group I) showed no evidence of cardiomyopathy. The 56% of patients who did exhibit transient or persistent evidence of cardiomyopathy (groups II and III) had received ADM on similar schedules and in equivalent doses. Factors responsible for variation in sensitivity to ADM are incompletely understood. Although age and a history of previous heart disease do not appear to affect sensitivity to the cardiotoxic action of ADM, pre-existing left ventricular dysfunction as evidenced by elevated baseline PEP:LVET ratios does appear to have an adverse

effect. Mean baseline values for groups II and III were significantly greater than the mean baseline for group I although the mean values for each group were in the normal range. Furthermore, four of the nine patients who developed congestive heart failure had abnormal baseline PEP:LVET ratios.

Mediastinal irradiation also appears to be associated with a higher incidence of cardiomyopathy. All patients with mediastinal irradiation were in that category of patients with persistently or progressively abnormal PEP:LVET ratios (group III). This finding agrees with others that radiotherapy to the heart increases the risk of failure associated with ADM therapy (3,7). The suggestion that cyclophosphamide also may enhance ADM-induced cardiomyopathy (3,7) is not supported by the present study. Whether different doses and schedules of cyclophosphamide therapy are important for its suggested cardiotoxic effect remains to be determined.

Congestive heart failure in the present study was more frequent but was milder than in most previous reports of ADM-induced cardiotoxicity (7). Earlier studies have emphasized the rarity of failure at total doses of ADM < 550 mg/m^2 and the fulminant nature of the failure when it occurred at doses > 550 mg/m^2 (1,7). Congestive heart failure at lower doses has been recognized, however, for ADM and daunorubicin, and it has not always been fatal (1,2,7). The more frequent occurrence of failure in the present study, especially at low total doses of ADM (13.6% at doses < 550 mg/m^2), and its usual mildness suggest that the diagnosis was made earlier than in other studies. Although the diagnosis of heart failure was made by physicians who were not directly involved in this study, the STI information was available to them and may have prompted more careful examination. Review of patient records confirms the diagnosis of failure which was based on the usual clinical criteria including weight gain and clinical response to diuretics and digitalis.

Our results show that patients with ADM-induced heart failure do respond to the usual treatment of bed rest, diuretics, and digitalis. Presumably, this responsiveness relates to early recognition of the failure.

Using STI, the present study has identified a group of patients who are more likely to develop heart failure and two characteristics, ie, abnormal baseline PEP:LVET ratio and mediastinal irradiation, which make a patient more sensitive to ADM-induced cardiomyopathy. Since more than half of the patients in groups II and III did not develop congestive heart failure, abnormal STI alone cannot be taken as an indication to terminate ADM therapy.

An abnormal PEP:LVET ratio, however, does indicate left ventricular damage. Not only may STI assist in the management of patients receiving ADM, but they will also be of value in assessing the efficacy of strategies designed to prevent or ameliorate anthracycline cardiotoxicity. Because the incidence of abnormal STI is high, studies in man using this noninvasive technique will more readily detect any beneficial effect of putative protective agents (such as α-tocopherol [8] and anthracycline analogs [9]) or different dose schedules (10) than those trials in man employing congestive heart failure as an endpoint. Endomyocardial biopsy appears to be an even more sensitive indicator of myocardial injury caused by ADM, but application of this technique probably will be limited because of its invasiveness (3).

Why approximately half of the patients treated with equivalent doses of ADM showed no left ventricular damage as judged by the STI remains incompletely understood. Differences in metabolism of ADM might account at least in part for such variation. Our preliminary results in rats (fig 4) indicate that radiolabeled ADM is not preferentially taken up by the heart. Other studies have shown comparable tissue distribution of ADM in the rat, hamster, and rabbit with metabolite formation (11). This evidence suggests that the heart may suffer damage partially as a result of ineffective repair mechanisms compared to other tissues. Even if this catholic distribution proves to be true in man, correlation of STI with the metabolism of this radiolabeled compound may show a difference in the metabolism of the drug between the groups with normal and abnormal STI. Other correlations such as the ability to detoxify oxygen radicals in model systems (12) with PEP:LVET ratios may provide further clues to understanding ADM-induced cardiotoxicity.

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Subclinical Adriamycin Cardiotoxicity: Detection by Timing the Arterial Sounds

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SUMMARY

"Sphygmo-Recording," a noninvasive method for timing the arterial pulse wave contour, provides a measurement (QK_d interval) which reflects changes in myocardial contractility and stroke output. The QK_d interval, ie, the time between the onset of the QRS complex (Q) and the onset of the Korotkoff sounds (K) at the brachial artery at diastolic pressure (d), is the sum of the cardiac pre-ejection period and the pulse transmission time. Serial QK_d intervals were done in patients receiving adriamycin (ADM) alone, in sequence with other chemotherapy, in combination chemotherapy, and in combination with radiotherapy. The QK_d interval was significantly prolonged (> 30 msec) within 1–3 weeks after ADM therapy alone or in combination therapy in > 50% of patients after the first dose and subsequently. Although similar changes were seen in patients receiving ADM in combination with cyclophosphamide, vincristine, and mediastinal radiotherapy, these patients often showed repeated and sustained QK_d elevations. The QK_d interval returned to baseline in most patients 2–4 months after stopping ADM. Four of seven patients receiving > 550 mg/m² of ADM developed congestive heart failure. In three patients, the QK_d interval failed to return to baseline values during ADM therapy 1–3 months prior to any other evidence of heart failure. In the fourth patient, ADM was stopped prior to heart failure after the QK_d failed to return toward baseline levels; the QK_d returned to normal for 4 months but abruptly increased in association with severe congestive heart failure. The QK_d interval appears to reflect subclinical ADM cardiotoxicity. Although weekly serial QK_d measurements may be useful in more accurately predicting clinical cardiomyopathy in patients receiving > 550 mg/m², it is not specific nor absolutely reliable.

[Cancer Treat Rep 62:901–905, 1978]

Prediction of adriamycin (ADM) cardiotoxicity with congestive heart failure in the individual patient continues to elude us. Although there is currently no test available which allows one to safely and confidently exceed dose limitations of ADM, several investigators utilizing different clinical techniques have contributed to our better understanding of ADM cardiomyopathy.

Cardiac systolic time intervals (STI), useful measures of ventricular performance in man, have been utilized prospectively in several patients receiving ADM (1,2). The STI (pre-ejection period [PEP] and left ventricular ejection time [LVET]) and the PEP:LVET ratio provide information about ventricular function (3). In heart failure the PEP lengthens, the LVET shortens, and the PEP:LVET increases. When measured frequently (3–6 weeks), it appears that the PEP:LVET increases transiently following ADM administration in some patients (1). As the cumulative dose of ADM increases, there is more profound reduction in left ventricular function and the recovery time is longer. Patients developing congestive heart failure had sustained elevation in PEP:LVET, which decreased with successful therapy for heart failure. Similar observations have been made by following patients with echocardiograms (4) and QK_d intervals (5,6). Unfortunately,

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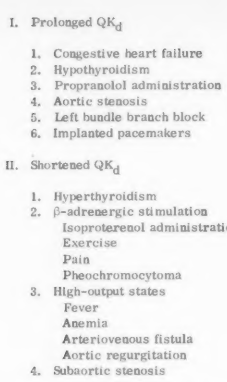

FIGURE 1.—QK_d interval in normal and disease states.

individual patients could not be reliably identified who absolutely would or would not experience heart failure with further doses of ADM. However, more has been learned about the physiologic effects of ADM on the heart and/or cardiovascular system and groups of patients can now be identified who may be at greater risk of developing heart failure.

The physiologic effect of ADM may be evaluated by assessing changes in myocardial contractility and stroke output by use of the noninvasive technique of Sphygmo-Recording (7–9). Sphygmo-Recording measures the time interval between the onset of the QRS complex (Q) of the electrocardiogram (EKG) and the arrival of the pulse at the brachial artery, as detected by the generation of arterial Korotkoff sounds (K) at the antecubital fossa during measurement of arterial blood pressure (diastolic [d] or systolic [s]). The QK_d interval can be recorded on any two-channel phonocardiogram (10) or on a properly modified cathode-ray oscilloscope (11). In normal adults < 70 years old, the QK_d interval has been shown to be limited to a narrow range, 205 ± 12 msec (9). The QK_d and pulse wave contour provide information regarding cardiovascular function in a variety of normal and disease states (12–15) (fig 1). The QK_d is the sum of the cardiac PEP and the pulse transmission time to the brachial artery. The QK_d and PEP showed a correlation ($r = 0.95$) in a coronary care unit study (16). Thus the QK_d, like the PEP, is a dynamic measurement which also reflects myocardial contractility as well as stroke output and arterial peripheral vascular tone. I report here a summary of results of prospective studies utilizing the QK_d interval for monitoring patients receiving ADM.

METHODS AND MATERIALS

The QK_d recordings in these studies were obtained by Sphygmo-Recorder Model SR250 of the City of Hope Medical Center, Electronics Instrumentation Division.[2] The pulse wave contour and QK_d interval were displayed automatically on the face of a storage oscilloscope and then photographed by a Polaroid camera. The means of triplicate measurement were used. Chest roentgenograms, EKGs, and physical examinations were also serially followed. The maximum change in the QK_d interval above pretreatment baseline after each course of chemotherapy was noted for each patient. Serial QK_d intervals, usually every week or every 2 weeks, were obtained on several groups of patients who were being treated at the Clinical Center of the National Institutes of Health (Bethesda, Md). Patients receiving chemotherapy other than ADM and normal volunteers were followed at comparable times as controls.

RESULTS

Controls

There were 23 control subjects followed. In 12 patients with sarcoma receiving chemotherapy other than ADM and in 11 normal volunteers, frequent serial measurements rarely showed changes in QK_d intervals > 30 msec. The between-day variability for any one subject was 14 msec. Therefore, we regarded a change in the QK_d of ≥ 30 msec as a "significant" change ($P < 0.05$) representing more than two standard deviations of measurement error. The *mean* changes of QK_d from baseline were 12.8, 9.0, 2.9, 4.9, and 13.7 msec in the normal subjects measured serially.

Patients Receiving < 550 mg/m² of ADM

Fifty-one patients who were receiving cumulative doses of ADM of < 550 mg/m² were serially followed. Most of these patients were receiving ADM for the first time, although a few had received ADM > 3 months previously but with cumulative doses < 300 mg/m².

Thirty-two patients had Ewing's sarcoma and were receiving ADM (75 mg/m²) every 7 weeks in sequence with cyclophosphamide (40 mg/kg) and vincristine (1.4 mg/m²) as an adjuvant to radiother-

[2] Rodbard S, and Mount B. Method and apparatus for obtaining and displaying cardiovascular data. US Patent No. 3,773,033, 1973.

apy. In 22 of these patients followed weekly, the *mean* maximum increases of QK_d following each of three courses of ADM therapy were 24.0, 21.8, and 30.5 msec, respectively. The QK_d was increased > 30 msec in most patients 2–3 weeks following even the first dose of ADM. In most patients, the QK_d was near baseline pre-ADM levels by the time of the next course of ADM 7 weeks later. In ten patients with Ewing's sarcoma, the QK_d was measured only every 4–7 weeks. The changes of QK_d following each of these courses of ADM showed *mean* QK_d increases of 2.1, 7.0, and 9.1 msec which were comparable to control subjects. This reflects the fact that measurements were not frequent enough to detect the transient increase in the QK_d as seen in patients followed more frequently.

Nineteen patients with bronchogenic carcinoma receiving radiation therapy to the mediastinum combined with ADM (40 mg/m^2), cyclophosphamide (900–1500 mg/m^2), and vincristine (1.4 mg/m^2) were also followed. These patients received chemotherapy every 2–3 weeks. The increases of QK_d seen in these patients were similar to those seen in patients receiving ADM every 7 weeks. The *mean* increases of QK_d were 13.3, 31.3, and 26.4 msec following each of three courses of chemotherapy, respectively. The prolongation of QK_d after the second and third courses of chemotherapy was increased relative to the first. The QK_d did not return to baseline in most of these patients prior to subsequent courses of chemotherapy. Similar changes continued to occur in these patients for a total of five or six courses of chemotherapy, but none of these patients developed any signs of congestive heart failure, and their QK_d values returned to pretreatment baseline levels within 2–4 months after the termination of chemotherapy.

Four patients were studied during ADM infusions and daily for several days in order to determine when the QK_d was first increased. The QK_d, heart rate, blood pressure, and EKG were monitored continuously during a 15-minute infusion and immediately after infusion for 1 hour. No changes were detected. The first change in the QK_d was a 10-msec increase on Day 4 in two patients which increased to 25 and 50 msec by Day 8. The other two patients showed significant increases in the QK_d (30 and 35 msec) at 2 weeks.

In all patients receiving < 550 mg/m^2 of ADM there were no significant changes in the physical examinations of the heart, pulse rates, and chest roentgenograms. Two patients developed transient premature atrial beats and one developed premature ventricular beats but no other EKG abnormalities were noted.

Patients Receiving > 550 mg/m^2 of ADM

Seven patients who were receiving > 550 mg/m^2 of ADM were serially evaluated. All patients were previously treated with other drugs without continued benefit and their diseases were progressive and responsive to additional ADM. There were four patients with metastatic Ewing's sarcoma, two with metastatic breast carcinoma, and one with metastatic soft tissue sarcoma in this group. Four of these seven patients developed ADM cardiomyopathy and congestive heart failure (table 1).

The three patients who did *not* develop congestive heart failure received 750, 675, and 650 mg/m^2 (cumulative doses) of ADM before death occurred from other causes or before a change in their therapy due to progressive disease was made. In these three patients, QK_d values were quite similar to those in patients receiving low cumulative doses of ADM, ie, transient increases with a tendency to return toward baseline by the next course.

In the four patients who did develop congestive heart failure, the QK_d increased and failed to return to within 20–30 msec of baseline on subsequent days of ADM administration. A brief description of these patients is outlined in table 1.

In the first three patients in table 1 the QK_d failed to return to baseline values prior to the development of clinically detectable heart failure. In patient 4, ADM was stopped before clinically detectable heart failure when the QK_d failed to decrease toward baseline. The QK_d values subsequently decreased to baseline values. Unfortunately, abrupt congestive heart failure occurred 4 months after the last dose of ADM, despite a QK_d value near baseline several weeks prior to overt heart failure. Serial EKGs and chest roentgenograms were normal in these patients except during overt congestive heart failure.

DISCUSSION

The QK_d interval is a physiologic measurement which is *not* a specific myocardial or ventricular function test. The QK_d, like the standard STI, is subject to changes in the cardiovascular system other than direct myocardial changes. Variability of measurements can be due to anemia, fever, pain, increased metabolism, and arteriovenous shunting through tumor vascular beds. Nonetheless, changes both in standard STI (1) and in QK_d interval following ADM therapy suggest a physiologic effect directly related to ADM. Both STI (PEP:LVET) and QK_d show transitory increases 1–3 weeks following even the first dose of ADM in many patients. This

TABLE 1.—QK_d changes and clinical course of 4 patients with ADM cardiomyopathy

Patient No.	Diagnosis	QK_d findings	Dose (mg/m^2) of ADM at onset of clinical heart failure	EKG and chest roentgenogram findings	Outcome
1	Breast carcinoma	Increase of QK_d interval with failure to return to within 20 msec of previous baselines 3 mos prior to clinical heart failure	950	No changes until overt heart failure	Initial clinical improvement with decrease of QK_d; died later with chronic heart failure and progressive metastatic disease
2	Breast carcinoma	Same as above except 2 mos prior to clinical heart failure	600	No changes until overt heart failure	Recovery with medical therapy for heart failure
3	Ewing's sarcoma	Same as above except 1 mo prior to clinical heart failure	600	No changes until overt heart failure	Fulminant heart failure; cardiac histology and electron microscopy diagnosis of ADM cardiomyopathy
4	Ewing's sarcoma	Increase in QK_d interval with failure to return to baseline and ADM was stopped prior to clinical heart failure	680	No changes until overt heart failure	Fulminant heart failure suddenly 4 mos after last ADM dose despite earlier return to baseline QK_d levels

change will not be appreciated if measurements are made infrequently (4–7 weeks) because the values have returned to baseline levels. Patients receiving ADM every 3 weeks in association with cyclophosphamide and mediastinal radiotherapy have progressive increases in QK_d, but have not experienced clinical heart failure with doses up to 240 mg/m^2 in this study. Most patients had a return of their QK_d to baseline values between 2 and 4 months after the last ADM dose.

There are several factors which suggest that the changes in STI and QK_d are indicative of clinically occult myocardial damage. Studies in mice have shown a depression of DNA synthesis in the myocardium occurring 6–8 days after the administration of ADM (17). This effect was dose-dependent and temporally related to fatal cardiotoxicity. An autopsy study of patients who were receiving ADM in low cumulative doses and died of noncardiac causes showed a high incidence of histologic myocardial changes consistent with ADM cardiomyopathy, although of a lesser degree than in patients known to have ADM-related heart failure (18). Even more convincing information has been obtained by serial endomyocardial biopsies in patients receiving ADM (19). Histologic findings from mild to severe have correlated with the cumulative dose of ADM in patients free of the symptoms and signs of clinical heart failure. The final factor supporting the hypothesis that increases in STI (PEP:LVET) and QK_d are early reflections of myocardial damage comes from the observations that these measurements are persistently prolonged in some patients prior to the development of overt heart failure. Patients in this study receiving > 550 mg/m^2 of ADM provided a unique opportunity to observe changes in QK_d. Although there was a trend of elevated QK_d intervals which did not return to within 20–30 msec of baseline levels in those who eventually developed congestive heart failure, one patient abruptly developed heart failure in the absence of an elevated QK_d prior to overt heart failure. The QK_d interval or STI cannot reliably predict which patient will develop heart failure. This is particularly true for those

with "normal" values, as several patients are on record who soon afterward developed acute heart failure.

Although too few patients have been followed to make firm conclusions, in those patients receiving cumulative doses of ADM > 550 mg/m² with persistently elevated QK_d or STI (PEP:LVET), one should be aware of the apparent increased risk of clinical heart failure.

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Systolic Time Intervals in Monitoring for Anthracycline Cardiomyopathy in Pediatric Patients [1]

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SUMMARY

Systolic time intervals are of value in measuring left ventricular function. The ratio of the pre-ejection period to the left ventricular ejection time (PEP/LVET) was determined serially in 60 children with cancer receiving anthracycline drugs. Measurements were examined for their predictive value in determining incipient anthracycline cardiomyopathy. An increase in the PEP/LVET ratio was not followed by clinical failure in the majority of patients. Of two patients who developed presumed anthracycline cardiomyopathy, only one demonstrated an increase in the ratio prior to going into heart failure. The value of the PEP/LVET ratio in children for predicting anthracycline cardiomyopathy appears limited, based on the results of this study.

[Cancer Treat Rep 62:907–910, 1978]

Systolic time intervals (STI) determined from simultaneous recordings of the electrocardiogram (ECG), the phonocardiogram, and the carotid arterial pulse tracing are of demonstrated benefit in assessing left ventricular function. Studies by Garrard et al (1) established correlations between the pre-ejection period (PEP), the left ventricular ejection time (LVET), and the ratio of PEP to LVET on the one hand and the angiographically determined ejection fraction on the other. In additional studies, Weissler et al (2) demonstrated that the failing left ventricle is characterized by prolongation of the systolic PEP and a shortening of the LVET, resulting in an increase in the PEP/LVET ratio.

With increasing usage of adriamycin (ADM) and daunorubicin in the treatment of various malignant disorders, physicians have become quite aware of the various side effects of these two agents, a major side effect being dose-dependent cardiotoxicity. Of primary concern has been the frequent development of congestive heart failure (CHF) at total doses of anthracycline drugs > 450–600 mg/m^2 (3–5). Once present, the CHF may be difficult to manage, and it is fatal in a significant percentage of affected patients. In attempts to find noninvasive methods of monitoring for cardiotoxicity, STIs used as measurements of left ventricular function have received attention. Rinehart et al (6) found increased PEP/LVET ratios in eight of nine patients receiving cumulative doses of ADM totaling 310–540 mg/m^2 and in one of nine patients receiving less. Only patients with increased PEP/LVET ratios developed CHF. These investigators concluded that STIs might be of value in detecting early cardiotoxicity. Thirty-eight children were studied by Ulmer (7) who reached a similar conclusion.

The present study was begun to evaluate the usefulness of STIs, specifically the PEP/LVET ratio, in monitoring for early anthracycline cardiotoxicity in a group of pediatric cancer patients.

METHODS

The charts of all patients receiving or about to receive anthracycline drugs in a pediatric oncology clinic were reviewed over an 18-month period. Sixty patients ranging in age from 2 to 19 years with serial PEP/LVET measurements comprised the study group. Forty-seven patients were being

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TABLE 1.—Mean PEP/LVET in 60 patients receiving ADM or daunorubicin

Drug dose (mg/m²)	No thoracic radiation (42 patients)		Thoracic radiation (18 patients)	
	No. of patients	PEP/LVET	No. of patients	PEP/LVET
0	29	0.44	9	0.42
0–99	31	0.44	11	0.46
100–199	30	0.44	11	0.43
200–299	25	0.47	7	0.40
300–399	12	0.46	3	0.55
400–499	5	0.49	—	—

treated for a variety of solid tumors and 13 were undergoing therapy for acute leukemia. None of these patients were known to have pre-existing cardiac disease, although one had mild hypertension at diagnosis. Fifty-seven patients received ADM and three received daunorubicin. Eighteen patients received thoracic irradiation to a total dose ranging from 1300 to 4400 rads, with inclusion of all or part of the heart within the fields.

The PEP/LVET ratios were determined from simultaneous recordings of the ECG, the phonocardiogram, and the carotid arterial pulse tracing. Measurements were repeated at dose increments of approximately 100 mg/m². Studies were regularly obtained at 2–6-week intervals after a dose of drug, usually before the next scheduled administration. Occasionally more than one measurement was obtained between doses. Of the total of 60 patients, a group of 38 children and adolescents who had a baseline PEP/LVET ratio determined before therapy with ADM or daunorubicin and had at least one other measurement during therapy were selected for additional evaluation. The remaining 22 patients did not have a baseline study done, but each did have at least three serial measurements of the PEP/LVET ratio during treatment with anthracycline drugs.

RESULTS

Attempts were made to correlate increasing cumulative dosages of anthracycline drugs with changes in the PEP/LVET ratio and to establish the usefulness, if any, of the ratio in predicting incipient cardiomyopathy. Table 1 lists the mean PEP/LVET values at increasing dose intervals for the total group of 60 patients. There is an increase in the ratio for the nonirradiated group above a total dose of 200 mg/m² and an increase for the irradiated group above 300 mg/m². However, these increases are all less than twice the standard deviation of the mean PEP/LVET value for these patients prior to either anthracycline administration or thoracic irradiation (SD = 0.06). The baseline values prior to cardiotoxic therapy are somewhat higher than the values obtained for a group of normal pediatric patients (mean value, 0.31 ± 0.05) (8) or for normal adults (mean value, 0.35 ± 0.04) (1). The reason for this difference is not apparent.

TABLE 2.—Mean change in PEP/LVET in 38 patients receiving ADM or daunorubicin

Drug dose (mg/m²)	No thoracic radiation (29 patients)	Thoracic radiation (9 patients)
0–249	-0.01 (16)	+0.04 (9)
250–500	+0.07 (13)	—

The mean changes in the PEP/LVET ratio in the 38 patients with baseline studies are shown in table 2. Nonirradiated patients who received ≥ 250 mg/m² of the drug were noted to have a mean increase of 0.07 in their ratio. Compared to the group receiving < 250 mg/m², this was a significant difference ($P < 0.05$ by the Student's t test). However, this difference is also less than twice the standard deviation of PEP/LVET for patients prior to anthracycline therapy. A similar comparison was not performed for the irradiated group because none of the patients in that group with baseline studies received ≥ 250 mg/m² of the anthracycline drug. In comparing the nonirradiated patients receiving < 250 mg/m² to the irradiated patients receiving < 250 mg/m², the irradiated patients demonstrate a greater change, similar to that of the nonirradiated patients receiving ≥ 250 mg/m², but the change is not statistically significant.

The percentages of patients with increases in the PEP/LVET ratio from their baseline value are listed in table 3. Again, the group who received thoracic irradiation followed by a total dose of anthracycline drug < 250 mg/m² appeared similar to the nonirradiated group receiving ≥ 250 mg/m². Both of these groups yielded higher percentages of patients with increases in the ratio than did the nonirradiated group receiving < 250 mg/m². Again, the differences are not statistically significant.

TABLE 3.—% of patients receiving ADM or daunorubicin with positive deflections in PEP/LVET (38 patients)

Drug dose (mg/m^2)	No thoracic radiation (29 patients)	Thoracic radiation (9 patients)
0–249	47% (8/17)	67% (6/9)
250–500	75% (9/12)	—

Two of the 60 patients developed presumed ADM cardiomyopathy. The first patient was a 4-year-old boy with metastatic Wilms' tumor who was treated with vincristine, actinomycin D, ADM, oral cyclophosphamide, and thoracic irradiation. A total dose of 399 mg/m^2 of ADM was administered. Whole-lung irradiation was given to a dose of 1500 rads. Additional "postage stamp" irradiation was administered to individual metastatic sites. CHF developed approximately 2 months after completion of the ADM and while the patient was in remission from his tumor. Only with the onset of CHF did the PEP/LVET ratio markedly increase (from 0.40 to 0.55). The CHF proved refractory to treatment, and the patient died 3 months after the onset of failure.

The second patient was a 4-year-old boy with metastatic hepatoblastoma who was treated with actinomycin D, 5-fluorouracil, ADM, and DTIC. A total dose of 450 mg/m^2 of ADM was administered. One month after completion of the ADM course, CHF developed. An increase in the PEP/LVET ratio (from 0.40 to 0.47) was noted 3–4 weeks before the onset of CHF. A repeat study done 10 days prior to the onset of CHF showed a slight improvement (0.45). After a subsequent dose of ADM the ratio increased further (0.50), at which time CHF was noted.

The total group of 60 patients was reviewed in an attempt to find patients with at least one recorded value for the PEP/LVET ratio of ≥ 0.50. A measurement of this magnitude suggests significant left ventricular dysfunction. Four patients who had limb amputations were excluded because as a group they had slightly elevated baseline PEP/LVET ratios (mean value, 0.46). The reason for this is unclear; however, none of the four patients has had other evidence of cardiac dysfunction. Of the remaining 56 patients, 28 were noted to have at least one value for the PEP/LVET ratio of ≥ 0.50 (table 4). The followup on these 28 patients has ranged between 1 and 26 months, with a median time of 12 months and a mean time of 11.4 months. Of the 28 patients, 19 continued therapy with anthracycline drug; none has developed CHF. Nine patients stopped therapy after the increase was noted; two of these were in CHF, necessitating discontinuation of the drug. Among the 19 patients continuing therapy, most had decreases in the PEP/LVET ratio on subsequent testing. However, the values of a few patients have remained elevated and none of these patients has developed CHF. Eight of the total of 28 patients with a value of ≥ 0.50 were noted to have values consistently in that range. Only one patient developed CHF. Eight patients, five in the nonirradiated group and three in the irradiated group, were noted to have increases of ≥ 0.10 above their baseline ratios (0.10 = twice the standard deviation of the mean PEP/LVET for a normal pediatric population) (table 4). Followup on the eight patients ranges from 3 to 20 months, with a median time of 11.5 months and a mean time of 11.8 months. Six of eight patients demonstrated the same increases on subsequent testing; two patients have not yet had followup studies performed. Of the eight patients, five continued therapy despite the increase, two stopped therapy because of the increase, and one stopped therapy because it was completed. CHF has not developed in any of the eight patients.

TABLE 4.—Patient characteristics

Characteristic	PEP/LVET ≥ 0.50	Change in PEP/LVET ≥ 0.10
No. of patients	28	8
No. of patients continuing therapy	19	5
No. of patients continuing therapy and developing CHF	0	0
No. of patients stopping therapy	9	3
No. of patients stopping therapy and developing CHF	2*	0

*In each patient anthracycline drug was stopped because of clinical CHF. One of the 2 patients had an elevated ratio prior to developing CHF.

DISCUSSION

The PEP/LVET ratio has received attention as a noninvasive method of monitoring for early anthracycline cardiotoxicity. We find a slight increase in the mean PEP/LVET ratios of our patients with increasing cumulative anthracycline dose, particularly at doses > 200–300 mg/m^2. Perhaps with a larger number of patients or with a patient population receiving larger cumulative doses, the increases in the mean PEP/LVET ratios would become more significant.

For nonirradiated patients receiving ≥ 250 mg/m^2 of drug, the mean increase in the PEP/LVET ratio is significantly greater than for nonirradiated patients receiving less. A similar comparison could not be performed within the group receiving thoracic

irradiation since no patients who had a baseline PEP/LVET ratio measurement also received ≥ 250 mg/m² of drug.

Two patients developed presumed anthracycline cardiomyopathy, but in one of these patients the PEP/LVET ratio did not increase before CHF became clinically manifest. Most patients in this study with markedly increased ratios or with abnormal increases in the ratio, even when sustained, have not developed CHF.

It appears that the value of the PEP/LVET ratio for predicting anthracycline cardiotoxicity in children is limited by the following observations: prolongation of the ratio did not always precede CHF and prolongation was not followed by clinical failure in the majority of patients. Serial determinations of the PEP/LVET ratio in an individual patient may be of some value. Sustained elevations in the ratio should focus the physician's attention on further evaluation of the patient with other parameters of cardiac functional integrity.

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Systolic Time Intervals: An Effective Measure of Cardiac Function in Anthracycline-Induced Cardiomyopathy of Rabbits [1]

Harry J. Long [2,3,4,*]

SUMMARY

The laboratory rabbit appears to be an ideal animal model for the study of anthracycline-induced cardiomyopathy in that it exhibits a cumulative, dose-related, histologically similar lesion to that seen in man treated with the same drug. Quantification of this cardiomyopathy with respect to total cumulative drug dose has been limited to histologic criteria, a cumbersome method which necessitates killing the study animal. With the intent of adapting noninvasive cardiac function studies, previously proven in man, to the rabbit, serial systolic time interval measurements in normal control and adriamycin (ADM)-treated rabbits are simple, easily performed, and readily reproducible, and accurately reflect physiologic cardiac function. In the rabbit, PEP:LVET ratios > 0.447 indicate significant ventricular dysfunction and are consistently seen at cumulative doses of ADM > 300 mg/m^2.

[Cancer Treat Rep 62:911–914, 1978]

The "ideal" experimental animal model for anthracycline-induced cardiotoxicity has been previously characterized as one which:

"*a.* exhibits a cardiomyopathy which progresses to congestive heart failure;
b. has measurable clinicopathologic parameters with reasonable endpoints;
c. exhibits total dose-related cardiomyopathy;
d. is a result of multiple iv injections;
e. exhibits pharmacokinetics similar to those in man;
f. has a high, reproducible degree of incidence (> 50%);
g. exhibits extracardiac toxicity similar to that in man; and
h. is manageable with respect to size, temperament, care, housing, and availability of tissues and body fluids for study" (1).

Only the laboratory rabbit best fulfills all of the above criteria. Histopathologic criteria for scoring the severity of anthracycline-induced cardiomyopathy have been developed (2,3) but are less than satisfactory. Pathologic criteria are time consuming and cumbersome, and require meticulous tissue collection, preparation, and review. Most importantly, histopathologic scoring necessitates killing the test animal. Thus, long-term serial studies cannot be performed on individual animals and we must use large numbers of animals which are killed serially, a factor which greatly increases the cost and complexity of experiments screening for less cardiotoxic anthracycline analogs and testing for cardioprotective agents.

Serial measurement of electrocardiograms (ECG) with summation of QRS voltage in the limb leads (4), systolic time interval measurement (5), and echocardiography with calculation of left ventricular ejection fraction (6) have been reported to correlate with the development of anthracycline-induced cardiomyopathy in man when applied serially.

Experimental trials were begun to determine the feasibility of adapting ECG criteria, echocardiography, and systolic time interval recording to the

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[3]The author gratefully acknowledges the technical assistance of HM2 Jerry Johnson and Emma Hartman in adapting systolic time interval measurement to the laboratory rabbit.

[4]Opinions or assertions expressed herein are those of the author and are not to be construed as official or as reflecting the views of the Navy Department or the naval service at large.

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serial study of adriamycin (ADM)-induced cardiomyopathy in the rabbit. ECG criteria were abandoned as nonspecific and difficult to standardize. Echocardiography was abandoned because it required excessive technician time and had low reproducibility with adequate quality tracings obtained only 50% of the time. Systolic time interval recording proved simple, accurate, and readily reproducible in diagnosing ventricular dysfunction in the rabbit.

MATERIALS AND METHODS

Twenty female New Zealand white rabbits, 8–10 weeks of age (mean weight, 2.4 kg), were divided into two study groups. Group A consisted of eight rabbits and served as the normal control. Group B included 12 rabbits, each of which received 40 mg/m^2 of ADM once weekly by rapid iv bolus into the lateral ear vein. Body surface area (BSA) was calculated according to the formula, BSA in cm^2 = $56.33\ W^{0.436}$, where W = weight in grams (7).

All animals were examined and weighed once weekly. Cbc counts were obtained weekly from the lateral ear vein and monitored for hematologic toxicity.

Each rabbit was anesthetized 10 minutes prior to systolic time interval measurement with 40 mg/kg im of ketamine hydrochloride, a dose which has been demonstrated to provide excellent anesthesia with minimal effect on respiratory or cardiac function (8).

Systolic time interval recordings were obtained once weekly in previously anesthetized and restrained supine rabbits. Phonocardiogram recordings were obtained using an Electronics for Medicine Model PSA-23 pulse sound microphone positioned over the left sternal border and filtered for sensitivity at 200–500 Hz. Carotid pulse wave forms were obtained by gently positioning the bare diaphragm of a statham P23Db strain gauge transducer over the skin covering the right carotid artery of the extended neck of the rabbit. The pressure amplifier was adjusted for sensitivity in the 0–10-mm mercury range. ECG was recorded in the standard limb leads using fine needle electrodes placed subcutaneously and with the low limit filter set at 0.1 mv and the high-limit filter set at 20 mv. Simultaneous recording of the phonocardiogram, the carotid pulse wave form, and the ECG was performed photographically on a multichannel Electronics for Medicine Model DR-12 recorder at a paper speed of 200 mm/second.

Pre-ejection period (PEP), left ventricular ejection time (LVET), PEP:LVET ratio, QS2 interval, and heart rate were calculated as previously described by Weissler et al (9,10). Normal systolic time intervals were determined serially in the group A rabbits with the inclusion of pretreatment values of the group B rabbits and an additional 15 rabbits who subsequently received mediastinal irradiation and ADM.

At termination of study or premature death, each animal underwent necropsy, and cross-sections of the cardiac ventricles were examined histologically for evidence of anthracycline-induced cardiomyopathy with hematoxylin-eosin and Masson-trichrome stains.

Statistical analysis was performed using the paired Student's t test with two tails.

RESULTS

Normal values of PEP, LVET, PEP:LVET ratio, and heart rate were obtained from 144 separate recordings in 35 rabbits. Mean normal systolic time interval values are represented in table 1. Serial systolic time interval recordings in the eight group A rabbits failed to demonstrate any significant variation over the 140 days of the study even though the rabbits increased in size (mean weight gain, 1.5 kg) as represented in figure 1.

Significant variations of PEP and LVET with respect to heart rate were observed according to the linear regression relationships noted in table 1. The correlation coefficient for the relationship of LVET to heart rate is highly significant. The PEP:LVET ratio corrects internally for variations due to heart rate, therefore PEP and LVET are not corrected for heart rate prior to calculation of the PEP:LVET ratio.

Figure 2 represents the mean ± SD for the PEP:LVET ratios of the 12 ADM-treated rabbits plotted serially with respect to total cumulative ADM dose. The PEP:LVET ratio became abnormal after a total cumulative dose of ADM of 200 mg/m^2. At 240 mg/m^2, the PEP:LVET ratio of 0.447 indicates significant left ventricular dysfunction compared to the normal controls ($P < 0.01$) with progressive dysfunction at higher cumulative doses.

TABLE 1.—Normal values*

	Mean value†
Heart rate	262/min
PEP ± SD	0.037 ± 0.007
LVET ± SD	0.109 ± 0.010
PEP:LVET ± SD	0.341 ± 0.066

*Determined from 144 recordings.

†PEP = 0.056–0.0000696 HR, r = 0.327; LVET = 0.171–0.000238 HR, r = 0.743.

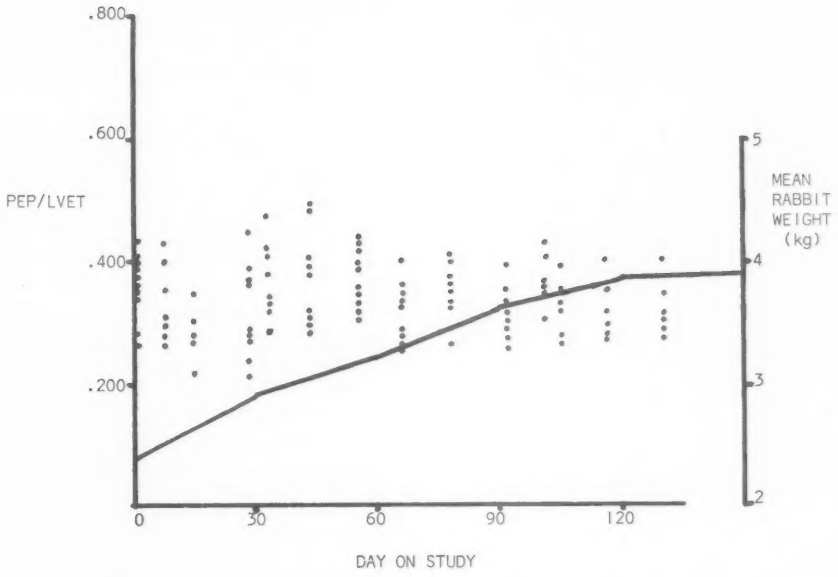

FIGURE 1.—Relationship of PEP:LVET ratio (scattergram) and body weight (solid line) to time in study.

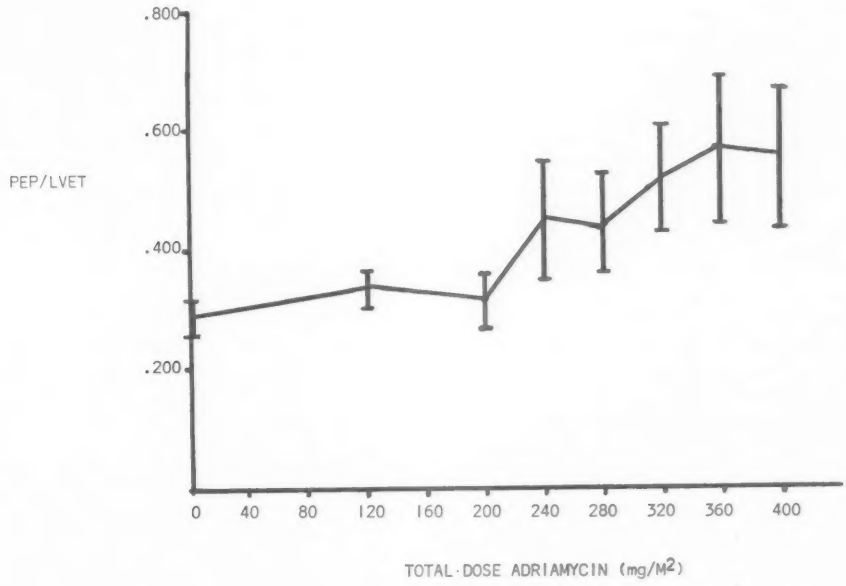

FIGURE 2.—Mean PEP:LVET ratio ± SD for group B rabbits serially plotted against total cumulative dose of ADM.

Dependent edema and weakness were universally seen in all rabbits when the PEP:LVET ratio was > 0.500, and acute pulmonary edema was evident when the PEP:LVET ratio was > 0.650. At necropsy, all of the ADM-treated rabbits exhibited pulmonary congestion, congestive hepatomegaly, massive ascites, pleural effusions, and tissue edema.

Histologic appearance of the right and left ventricles confirmed severe ADM cardiomyopathy with marked myofiber degeneration, myolysis, interstitial fibrosis, and extensive myocyte vesiculation diffusely involving the entire myocardium.

DISCUSSION

Systolic time interval measurements do not provide a linear correlation with the total cumulative dose of ADM or the degree of anthracycline-induced cardiomyopathy. Systolic time intervals measure the functional status of the cardiac ventricles and not the histologic development of cardiomyopathy. The myocardium compensates for the loss of myocyte numbers by increasing the efficiency of contraction of the remaining myocytes until it can no longer compensate. A PEP:LVET ratio > 0.447 indicates failure of this compensatory mechanism and correlates with severe cardiomyopathy.

Although this study is small and involves only a single, weekly high-dose ADM regimen, it clearly establishes that serial systolic time interval recording is a simple, readily reproducible, and highly accurate noninvasive measurement that correlates with the development of clinical and histologic evidence of anthracycline-induced cardiomyopathy in laboratory rabbits. In addition, it establishes the mean normal values for PEP, LVET, and PEP:LVET ratio in the rabbit, and the linear regression relationship between PEP, LVET, and heart rate in the rabbit. It also establishes that systolic time interval measurements, when applied serially during anthracycline treatment of rabbits, provide a numerical value for cardiac function which may be applied to statistical comparison studies of newer anthracycline analogs or in studies looking for cardioprotective agents.

Most importantly, the addition of serial systolic time interval recording to future studies of anthracycline-induced cardiomyopathy will permit a marked reduction in the number of rabbits necessary to develop dose-response relationships, thus reducing the cost and time required to complete the studies.

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Noninvasive Cardiac Evaluation of Patients Receiving Adriamycin [1]

Gordon A. Ewy,* Stephen E. Jones, Mark J. Friedman, John Gaines, and Debbie Cruze [2]

The anthracycline antibiotic, adriamycin (ADM), has been shown to be an important addition to the oncologist's drug armamentarium because it is effective when given singly or in combination against a wide variety of human cancers (1). Although side effects associated with the use of other anticancer drugs, ie, myelosuppression, mucositis, hair loss, and nausea and vomiting, are observed with ADM, the major dose-limiting side effect which is unique for this class of compounds is the development of cardiomyopathy.

Studies by Lefrak et al and Cortes et al have shown that this is not an idiosyncratic or hypersensitive phenomenon, but is directly related to dose (2,3). The incidence of cardiomyopathy increases markedly when the total dose of ADM is > 550 mg/m^2. ADM cardiomyopathy shares the clinical features of other congestive cardiomyopathies with predominant symptoms and signs of congestive heart failure. Rarely, arrhythmias may occur. The patients may symptomatically improve with standard modes of therapy (sodium restriction, bed rest, diuretics, and digitalis), but the underlying cardiomyopathy is generally felt to be irreversible and even fatal. Currently, the only established means of avoiding this cardiotoxicity is by limiting the total lifetime dose of ADM.

There have been several attempts to use both noninvasive and invasive techniques to detect subclinical cardiac damage from ADM before patients develop overt heart failure. These techniques are reviewed in this and other papers in this issue. The measurement of systolic time intervals from phonocardiograms and the calculation of frontal plane voltage from electrocardiograms (ECGs) are examples of noninvasive techniques that show promise (4,5). Additionally, investigators at Stanford University have proposed the use of serial endomyocardial biopsies via the venous circulation as a potential invasive means of identifying early myocardial damage (6).

During the course of evaluating patients with ADM cardiomyopathy, we were able to demonstrate the development of abnormal ventricular function by echocardiography (7). In 1974, we began a prospective study of the usefulness of this technique in relation to other noninvasive techniques in assessing ventricular function in patients receiving ADM therapy.

METHODS

Echocardiograms, phonocardiograms, systolic time intervals, and ECGs have been recorded in adult patients with biopsy-proven cancer. Initially, all patients who were receiving or had received ADM were studied. Subsequently, all patients considered for therapy had baseline (control or zero dose) studies and if ADM was initiated, serial studies were performed at 3-month intervals. Almost all of the patients treated at the University of Arizona received combination chemotherapy with ADM and cyclophosphamide. As of August 1977, 352 patients had been studied. The mean age of the patients was 55 years. Forty-five percent of the patients had breast cancer, 12% had gynecologic cancer, 10% had lung cancer, and the remainder had a variety of other solid tumors as well as hematologic malignancies.

Echocardiograms were obtained with a commercial echocardiographic unit (Ekoline-21) having a repetition rate of 1000 pulses/second utilizing a 2.25 mHz transducer with a 13-mm diameter crystal. The echocardiograms were recorded on a Honeywell 1856 strip chart recorder with simultaneous ECG reference lead. The patients were examined in the supine or the slightly left lateral position with the transducer at the left sternal border in the interspace where the mitral valve echos were seen best. The cardiac echos were continuously recorded as the transducer was tilted slowly through an arc with the ultrasonic beam traveling from the area of the aortic valve to the left ventricle. Figure 1 illustrates a normal left ventricular echocardiogram and demonstrates how the measurements were made. Left ventricular internal diameter (LVID)

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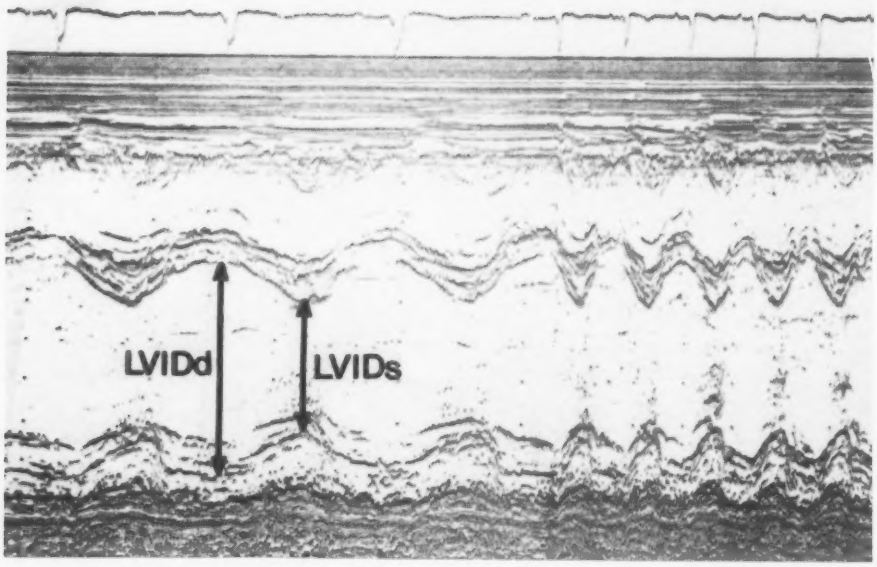

FIGURE 1.—Echocardiogram of left ventricle recorded with the transducer aimed just caudad to the mitral leaflets. Recording speed which is initially 50 mm/sec is changed to 25 mm/sec.

measurements were taken from the left side of the interventricular septum to the posterior left ventricular endocardium, both during end diastole (LVIDd) and end systole (LVIDs). The left ventricular diastolic dimension was made at the QRS complex and the systolic measurements were made on a line extending vertically from the most anterior portion of the posterior left ventricular endocardial surface. The measurements were used to calculate the echocardiographic ejection fraction (ECHO-EF) as follows:

$$EF = \frac{(LVIDd)^3 - (LVIDs)^3}{(LVIDd)^3}.$$

Systolic time intervals were recorded (fig 2) by the method of Weissler and associates (8). Standard 12-lead ECGs were recorded utilizing a Marquette three-channel ECG model 2000 series.

The clinical features of the patients and the measurements from the echocardiogram, phonocardiogram, and ECG were entered into a computer and analyzed with the statistical package for the social sciences on a CDC 6400 computer (9). Initial bivariant analysis revealed that total ADM dose, sex, thoracic radiation, and cardiac risk factors appear to affect certain parameters. These factors were then subjected to a regression technique equivalent to multi-way analysis of variants that permits simultaneous assessment of separate and interacting effects of the factors considered.

To date, our data have been analyzed in two ways. The first involves the echocardiographic evaluation of nonserial measurements at various ADM dose levels. The second involves an evaluation of serial changes in noninvasive parameters.

RESULTS

Nonserial Measurements

When we first began our echocardiographic study of patients receiving ADM, we made an echocardiographic recording from each patient. We thus had a large number of patients with cancer who had not

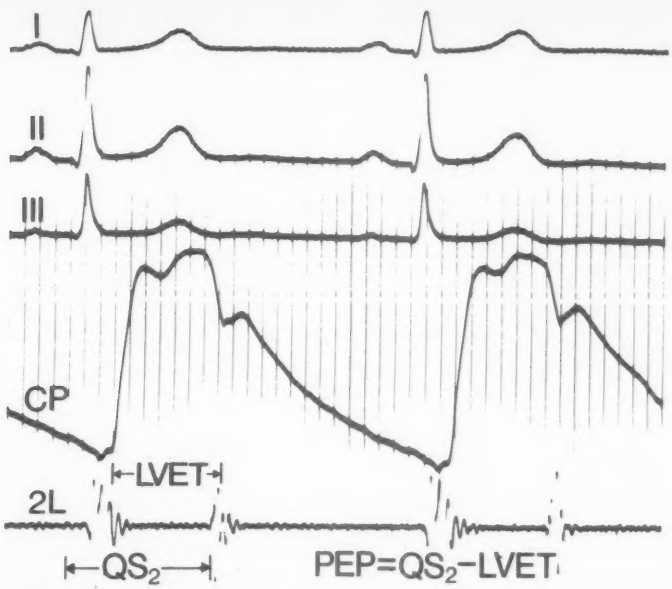

FIGURE 2.—Measurements of systolic time intervals are obtained from simultaneous high-speed (minimum of 100 mm/sec) recordings of the phonocardiogram from the 2nd left intercostal space, the indirect carotid pulsation, and leads I, II, and III of the reference ECG. Time lines are 0.04 sec. LVET is the time from the onset of the carotid pulse to the dicrotic notch. PEP is the time from the onset of electrical depolarization to the onset of left ventricular ejection. Since there is time delay in the transmission of the systolic impulse to the carotids, the PEP cannot be measured directly, but has to be obtained by subtracting the LVET from the total electrical mechanical systole (QS2). There is no significant delay in the transmission of the sound or electrical deflections.

received ADM therapy and a number of recordings from patients who had received either small, intermediate, or high total doses of ADM. There were no serial measurements in this group of patients. An analysis of the echocardiographic findings in these patients revealed no consistent abnormality in patients receiving < 450 mg/m² of ADM. A comparison of the echocardiographic findings of 185 patients studied prior to ADM therapy with the results of 27 patients who had received > 450 mg/m² (table 1) revealed that in patients who did not receive previous or concurrent thoracic radiation, there was a significant increase in LVIDs corrected for body surface area, but not a significant increase in LVIDd. There was a small but significant decrease in left ventricular ECHO-EF. In contrast, there was

TABLE 1.—Nonpaired echocardiographic measurements in adult cancer patients receiving ADM*

Measurement	ADM dose		*P* value
	No thoracic radiation		
	0 dose (135 patients)	≥ 450 mg/m² (16 patients)	
LVIDd/m²	38 ± 5	39 ± 7	Not significant
LVIDs/m²	25 ± 4	29 ± 7	< 0.01
ECHO-EF	0.72 ± 0.09	0.60 ± 0.15	< 0.01
	Thoracic radiation		
	0 dose (50 patients)	≥ 450 mg/m² (11 patients)	
LVIDd/m²	38 ± 6	43 ± 7	< 0.05
LVIDs/m²	24 ± 4	36 ± 9	< 0.01
ECHO-EF	0.75 ± 0.08	0.46 ± 0.19	< 0.001

* All measurements are expressed as mean ± 1 SD.

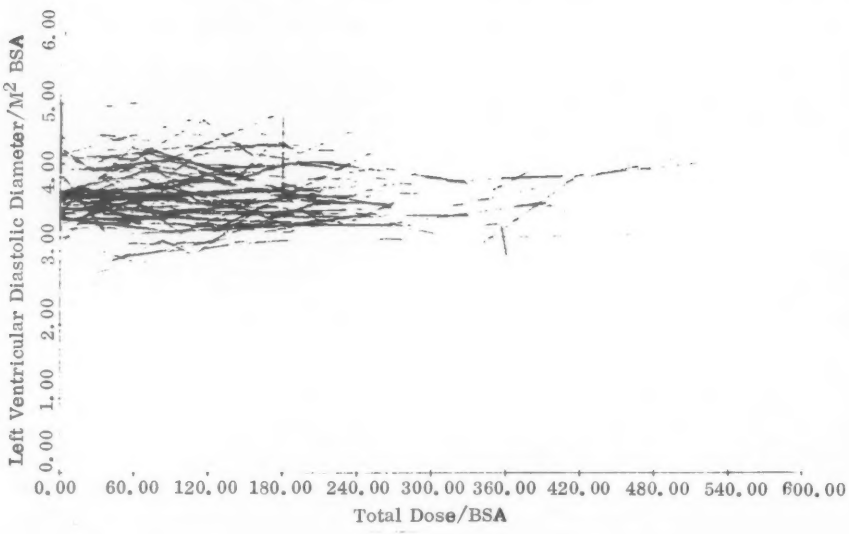

FIGURE 3.—Echocardiographically derived LVIDd corrected for body surface area plotted against dose of ADM. Lines connect serial measurements on the same patient.

a significant increase in both systolic and diastolic LVID and a marked decrease in ECHO-EF in those patients who had received both thoracic irradiation and high cumulative doses of ADM. Thus, echocardiographic measurements of ventricular function demonstrated that thoracic radiation is one of the risk factors for the development of ADM cardiotoxicity.

Serial Measurements

It was possible to obtain technically satisfactory echocardiograms in 62% of adult patients with cancer. Since the primary purpose of this study was to compare the relative sensitivity and specificity of the various noninvasive tests, only data from patients in whom a satisfactory echocardiogram was obtained were analyzed. One hundred and twenty patients have been studied two or more times and were suitable for analysis of serial changes as of August 1977.

Plots of serial measurements of LVIDs, LVIDd, ECHO-EF, and systolic time intervals (PEP:LVET) are shown in figures 3–6.

A further analysis was carried out on a subset of these 120 patients. There were 58 patients in whom the first study was performed with an initial mean ADM dose of 16 ± 36 mg/m² and the last study at a mean dose of 440 ± 119 mg/m². The results of these serial measurements are given in table 2. The only significant change in echocardiographic measurements in these patients was a slight increase in the E point septal separation. There was a slight, but significant drop in the total frontal plane ECG voltage, and there was a slight, but significant increase in the PEP:LVET ratio.

Since all patients whose ECGs were analyzed also had technically satisfactory echocardiograms, we were provided with an opportunity to examine the effect of pericardial effusion on the analysis of total frontal ECG voltage. Forty-seven of the 58 patients had no evidence of pericardial effusion and had a mean percent drop in frontal plane QRS voltage of 10.5% between the first and last studies ($P < 0.01$). There were 11 asymptomatic patients who were found to have an occult pericardial effusion at either the initial, final, or both initial and final study. In these patients, there was only a 4.7% mean change in frontal plane voltage between

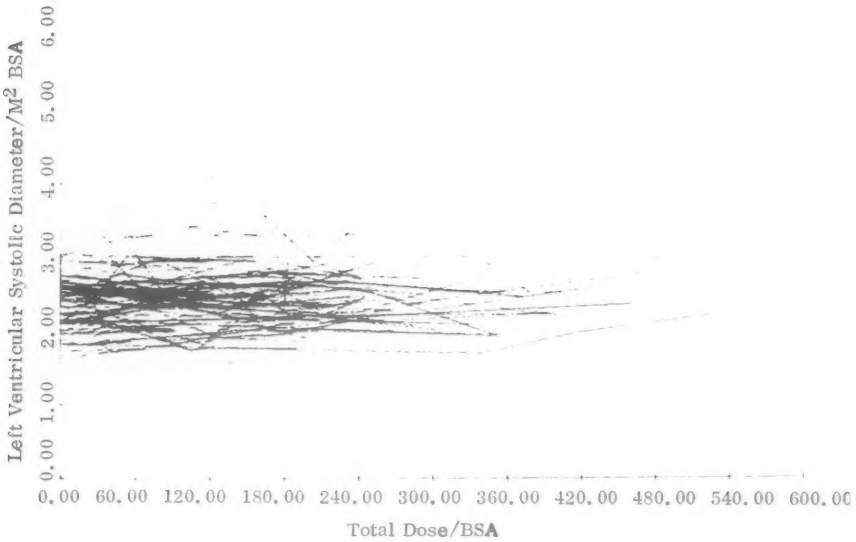

FIGURE 4.—Echocardiographically derived LVIDs corrected for body surface area plotted against dose of ADM. Lines connect serial measurements on the same patient.

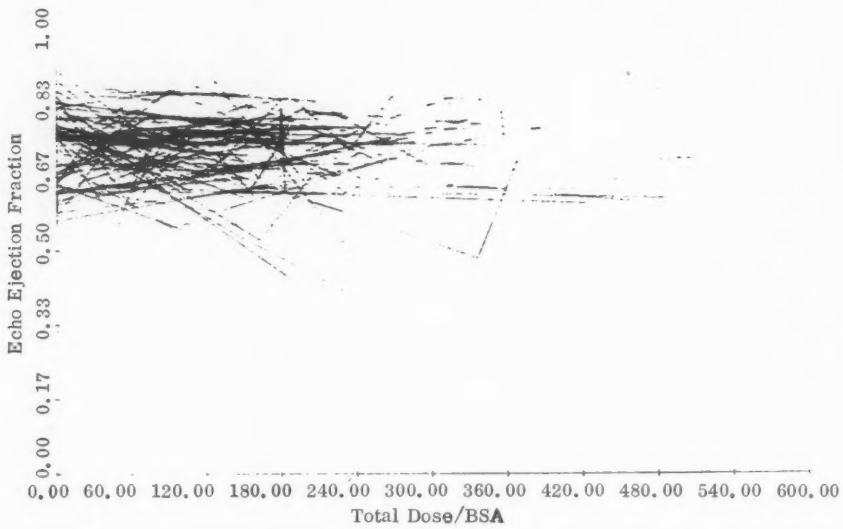

FIGURE 5.—Calculated ECHO-EF plotted against dose of ADM. Lines connect serial measurements on the same patient.

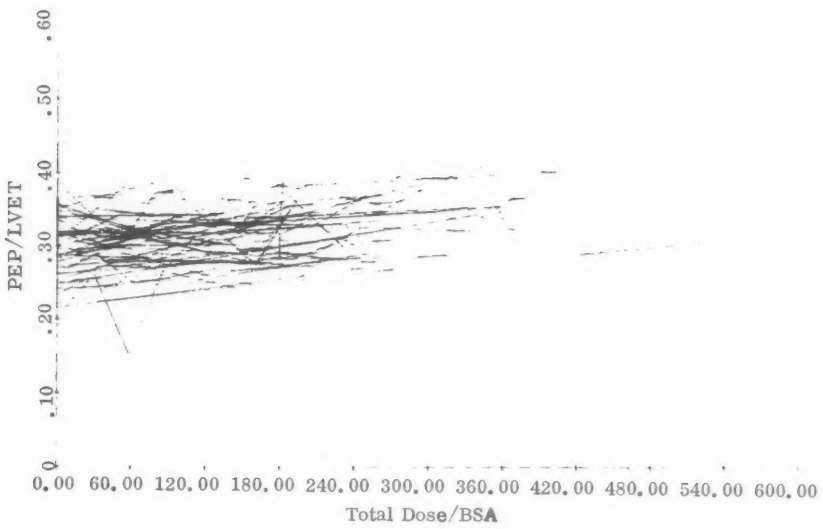

FIGURE 6.—Phonocardiographically derived ejection time indices (*see* fig 2) plotted against dose of ADM. Lines connect serial measurements on the same patient.

TABLE 2.—Noninvasive evaluation of cardiac function in adult cancer patients receiving ADM: serial observations in 58 patients with initial dose of 16 ± 36 mg/m² and final dose of 440 ± 119 mg/m²

Measurement*	Initial	Final	*P* value
Echocardiogram			
Left atrial diameter	2.98 cm	2.99 cm	NS†
LVIDd/m²	3.79 cm	3.85 cm	NS
LVIDs/m²	2.42 cm	2.46 cm	NS
% fractional shortening	36%	36%	NS
ECHO-EF	0.73	0.73	NS
E point septal separation	4.1 mm	4.8 mm	< 0.02
ECG			
Total frontal plane voltage	39.8	35.5	< 0.01
Systolic time intervals			
PEP:LVET	0.31	0.33	< 0.01

*All measurements are expressed as mean values.
†NS = not significant.

studies ($P = 0.20$). Thus, it appears that the presence of a pericardial effusion might interfere with the accurate assessment of changes in ECG frontal plane voltage caused by ADM administration.

DISCUSSION

Analysis of our initial nonserial studies by echocardiogram revealed two important factors. The first is that concomitant or previous thoracic radiation associated with a total cumulative dose of ADM > 450 mg/m^2 results in a marked deterioration of ventricular function as assessed by echocardiography. Second, the finding of an increased systolic dimension without a significant increase in diastolic diameter in patients receiving only ADM suggests that the initial mechanism of decreased cardiac output in patients with ADM therapy is a decreased contractility which results in a decrease in the systolic diameter and/or circumference prior to compensatory dilatation of the left ventricle.

Serial measurements comparing various noninvasive techniques indicate that there are slight but statistically significant changes in at least one measured parameter of the echocardiogram, systolic time intervals, and ECG. At the dose level studied, none of these noninvasive techniques appears to offer a unique advantage in terms of sensitivity or specificity over the others. However, it should be remembered that technically satisfactory echocardiograms could be obtained in about 62% of patients, which is in agreement with the findings of Popp (10). Thus, this factor eliminates echocardiography as a useful technique for monitoring about 40% of patients receiving ADM.

Our studies also suggest that the presence of a pericardial effusion may interfere in the accurate assessment of changes in frontal plane ECG voltage measurement, a technique for following patients advocated by others (5). For example, we found asymptomatic pericardial effusions in 11 (19%) of the 58 patients analyzed for serial changes. This observation, if confirmed in a larger number of patients, may impose an inherent limitation on the usefulness of monitoring serial ECG voltage in patients receiving ADM.

Thus, at the present time, each of the noninvasive methods of assessing ventricular function has advantages and disadvantages in certain patients and none of these techniques has yet proven to be superior to the others in terms of sensitivity or reliability in detecting occult heart disease. Our own efforts will focus on following these and other patients at higher doses of ADM with all of the noninvasive techniques so that we can eventually determine the optimal method of assessing subclinical ADM cardiomyopathy.

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Serial Studies of Cardiac Function in Patients Receiving Adriamycin [1]

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SUMMARY

A total of 283 adult and pediatric patients treated with drug combinations which include adriamycin (ADM) had at least one cardiac evaluation; 103 patients had two or more serial studies after a baseline evaluation. Changes in systolic time intervals, echocardiographically determined ejection fractions, and electrocardiographic voltage correlated with increasing cumulative ADM dosage. However, the incidence of congestive heart failure among these patients was < 2%. It is estimated that 22%–31% of these patients would not have completed a cumulative dose of > 450 mg/m² of ADM if the drug had been discontinued on the basis of these tests, using previously published criteria for cessation of treatment. Thus far, however, no adverse effects have been observed from the completion of planned courses of therapy. The clinical significance of serial changes in noninvasive tests is therefore uncertain. While such changes may reflect subclinical anthracycline cardiotoxicity and clinical cardiotoxicity can reliably be diagnosed, the utility of routine, serial noninvasive testing in planning conventional-dose anthracycline therapy is questionable.

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Anthracycline cardiomyopathy was first described as the abrupt onset of congestive heart failure (CHF) in patients given large cumulative doses of daunorubicin or adriamycin (ADM). In a review of the first 1800 patients treated with ADM (1), the incidence of cardiomyopathy as evidenced by CHF was noted to be < 1% when a total dose of ≤ 500 mg/m² had been given; however, after treatment with doses of 600–1000 mg/m², only 30%–40% of the patients developed significant CHF. Thus, it seemed possible that (*a*) some patients might be "resistant" to ADM cardiomyopathy or at least capable of tolerating larger doses than others, and (*b*) noninvasive tests of cardiac function might be used to determine appropriate dose limits for an individual patient.

One early report suggested that specific changes in the systolic time intervals (STI) were correlated with the subsequent appearance of CHF (2); that report provided part of the stimulus for this work, which was initiated in December 1974. In this study, serial echocardiograms, electrocardiograms (ECG), chest roentgenograms, and STIs were obtained to evaluate the usefulness of each of these modalities in detecting early or subclinical cardiomyopathy. Subsequent reports on the value of each of these tests have appeared (1,3). However, it is still not clear whether such noninvasive procedures can be used to guide a physician in the use of ADM in an individual patient.

MATERIALS AND METHODS

Patients selected for serial studies had a life expectancy of > 1 year. All adult women scheduled

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to receive ADM and cyclophosphamide on the adjuvant breast protocol, children with acute lymphatic leukemia receiving ADM after a vincristine/prednisone-induced remission, and patients with osteogenic sarcoma receiving adjuvant ADM and methotrexate were routinely included in this study. The dose schedule of ADM administration for these three groups was 45 mg/m^2 every 3 weeks, 30 mg/m^2 every 3 weeks, and 75 mg/m^2 every 4 weeks respectively. As a rule, these patients had a baseline evaluation before any drug therapy. Serial studies were also obtained in a fourth group of patients with a variety of different tumor types and treatment schedules; all of the patients in this last group had a baseline study before a cumulative dose of 200 mg/m^2 had been reached. Patients who had prior heart disease, prior anthracycline cardiomyopathy, or >200 mg/m^2 of ADM before their initial cardiac evaluation were treated as a separate group and were not included in analyses of serial studies.

Cardiac evaluations included: (*a*) measurement of STIs by standard techniques using simultaneous phonocardiograms, ECG, and carotid pulse tracing, (*b*) echocardiographic assessment of left ventricular volumes, cardiac output, and ejection fraction, and (*c*) measurement of heart size using a posteroanterior chest roentgenogram. The ratio of the pre-ejection period to the left ventricular ejection time (PEP/LVET), a standard phonocardiographic parameter of left ventricular function, was determined (4). The echocardiographic ejection fraction was calculated from left ventricular end-diastolic and end-systolic dimensions converted to volumes by the method of Teichholz et al (5) for adults and approximated in children by cubing the linear dimensions. ECG voltages were evaluated by summing the negative and positive deflection of all six limb leads and calculating a percent increase or decrease relative to the summed voltage of an ECG obtained before any therapy had been given or before 100 mg/m^2 cumulative dose of ADM had been administered.

Cardiac evaluation was usually done the same day the patient came to the clinic for ADM, but left ventricular function tests were always obtained before the drug was given to avoid possible acute effects of ADM on the heart. Patients treated with a dose of ≤ 60 mg/m^2/course were scheduled for cardiac evaluations just before a cumulative dose of 90, 180, 270, 360, and 450 mg/m^2 of ADM was reached; patients given >60 mg/m^2/course were studied just before a total dose of 150, 300, and 450 mg/m^2. All patients were scheduled for followup tests 3, 6, 12, and 24 months after the last dose of ADM.

Results of cardiac evaluations were forwarded to the primary care physician after each study was performed, but clinicians caring for these patients were discouraged from discontinuing the drug solely on the basis of an abnormal study.

In analyzing these data, two sets of tentative criteria for discontinuing ADM were developed. "Rigorous" criteria were those derived from previously published studies. The abnormal values were as follows: a PEP/LVET ratio >0.42 *and* an increase in this ratio ≥ 0.07 above the baseline if the baseline value was normal, or 0.05 above the baseline if it was abnormal (6); an ejection fraction <0.43 (3); and ECG voltages $<60\%$ of pretherapy values (1). "Nonrigorous" criteria were any values which deviated from the norm for the test by more than one standard deviation. In these laboratories these were any PEP/LVET ratio of >0.40 and/or an ejection fraction of <0.55. No such norms exist for serial ECGs.

Statistical analyses were performed using a Student's t test to determine the levels of significance. Data were computerized on a Digital Equipment Corporation PDP 10 using System 1022 and STATPAK routines.

RESULTS

A total of 283 patients ranging in age from 1 to 78 years were studied between December 19, 1974, and September 1, 1977; 854 left ventricular function studies were performed. All but 60 of these patients were prospectively entered in the study for serial evaluations; this included 62 patients with acute lymphatic leukemia, 31 patients receiving adjuvant treatment for osteogenic sarcoma, 24 patients receiving adjuvant treatment for breast cancer, and 106 patients receiving various other protocols. There are now 103 patients who have both completed therapy (usually with a cumulative dose of ADM >400 mg/m^2) and have had at least two cardiac evaluations. Sixty-one of these patients have had five or more serial studies.

Only two of the patients studied serially have had evidence of CHF clearly attributable to ADM cardiomyopathy. Two other patients have had transient episodes of CHF associated with a stress such as a large volume of iv fluid. These patients were treated with digoxin and diuretics; both were later able to function normally without cardiac drugs and had normal ejection fractions and STIs. It is assumed that these two patients had decreased cardiac reserve but not a true clinical cardiomyopathy by the usual criteria, eg, symptoms, abnormal physical signs, and radiographic cardiomegaly. One patient, 67 years of age, reportedly died with acute pulmonary edema and arrhythmia in another hos-

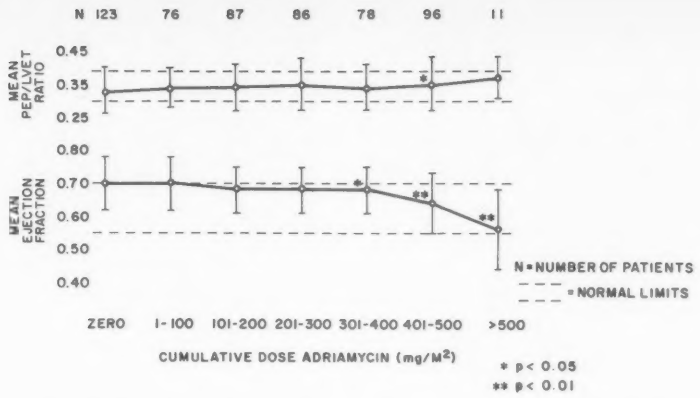

FIGURE 1.—Dose-related changes in left ventricular function parameters (all patients).

pital 6 months after completing adjuvant therapy for breast cancer; this patient had a recurrence of her cancer with a malignant pleural effusion. It is not clear if her death was related to an intrinsic cardiac abnormality. Thus, only two of the 103 patients studied prospectively from the time ADM therapy was initiated have developed an unequivocal cardiomyopathy.

Cardiomyopathy has been observed in an additional 12 patients treated at the Sidney Farber Cancer Institute during this study period, including five patients given cumulative doses well above 500 mg/m^2. Results of studies in these patients are not included in the group data presented in this analysis.

Population Trends of Cardiac Evaluations

PEP/LVET ratios, ejection fractions, and ECG voltage changes obtained from each patient were correlated with the dose of ADM which had been given prior to the time of each study. These values were pooled into seven groups. All studies obtained before any ADM was given were considered as one group. Studies obtained in patients who received at least one dose of ADM but no more than a total of 100 mg/m^2 were also grouped together. Other groupings, based on cumulative ADM dose, were 101–200, 201–300, 301–400, 401–500, and >500 mg/m^2. The mean PEP/LVET and ejection fraction for each of these groups are shown in figure 1. At no point do the mean values exceed the norms. When the mean values obtained at each dose interval are compared with the mean baseline value, however, it is found that the average PEP/LVET ratio increased significantly only among patients who had been given >400 mg/m^2 ($P < 0.05$). A significant fall in ejection fraction occurred after a cumulative dose of only 300 mg/m^2; values obtained in patients who received 401–500 and >500 mg/m^2 were further depressed ($P < 0.01$). These data were analyzed separately for various age groups and for each treatment group (ie, acute lymphatic leukemia, adjuvant osteogenic sarcoma, and adjuvant breast cancer). No significant differences in the trends observed for the entire patient population were noted in these various subgroupings.

The percentage of patients with varying degrees of abnormality in their STIs, ejection fractions, or ECG voltages are shown in figure 2. Nineteen percent of all patients had a baseline PEP/LVET ratio of >0.40; 7% were >0.45, and 2% were >0.50. The fraction of patients with an elevated PEP/LVET ratio did not appreciably change with increasing cumulative doses, but the percentage of patients with markedly abnormal values (>0.50) increased from 2.1% of the patients before any ADM was given to 6.4% of all patients who received >400 mg/m^2. None of these patients had persistent abnormalities; only three patients had PEP/LVET ratios >0.50 on more than one study.

Approximately 10% of the patients had baseline ejection fractions <0.60, and this increased to almost 20% of the patients who were given >400 mg/m^2 of ADM. The percentage of patients with an ejection fraction of <0.55 did not appreciably increase until the highest dose range when the proportion of patients with an unequivocal abnormality in this test increased to include 10% of all patients studied. Similarly, the fraction of the study population with an ECG voltage drop exceeding 40% was small until a dose of >400 mg/m^2 had been given; such ECG voltage depressions occurred in eight of 50 patients in this group. However, $\leq 20\%$ of the

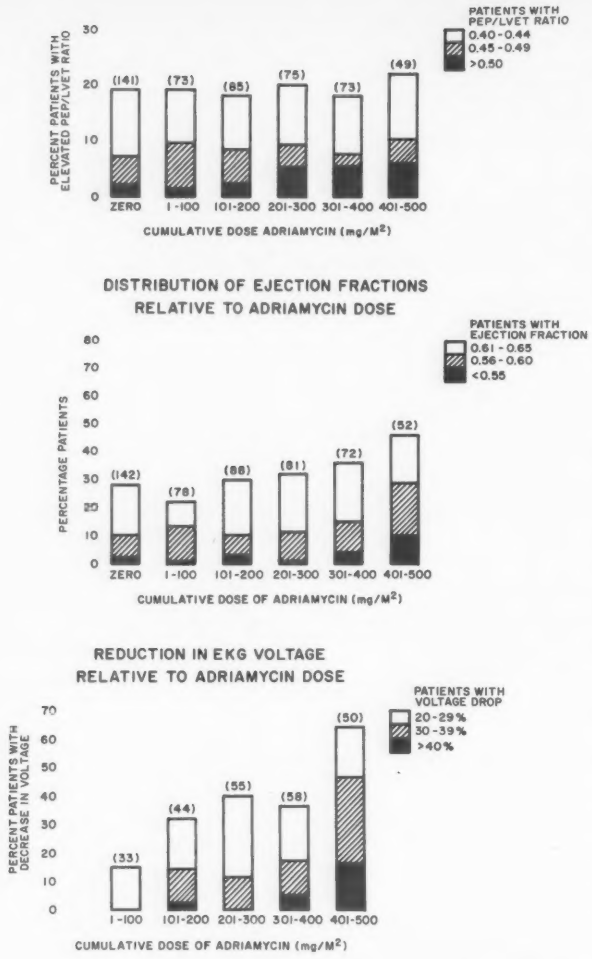

FIGURE 2.—Incidence of elevated PEP/LVET ratio relative to ADM dose.

patients had borderline voltage changes (a decrease of 30%–39% below baseline) before a cumulative dose of 400 mg/m² had been reached; 30% of the patients given > 400 mg/m² had such changes.

Individual Patient Evaluations

Since the number of patients who have developed CHF is still small, the cardiac profiles of the patients with clinical signs and symptoms have been carefully scrutinized and compared to those of asymptomatic patients. Several such profiles have been selected to illustrate the limitations of currently available criteria for discontinuing anthracycline therapy; these are shown in figure 3.

Patient 1, a 15-year-old girl with a histiocytic lymphoma, is now in complete remission after therapy which included vincristine, 6-mercaptopurine, methotrexate, and ADM. She has been followed for > 16 months following her last dose of ADM; she has never had symptoms, abnormalities on physical examination, or cardiomegaly on chest roentgenogram. However, after she had received a dose of 185 mg/m² of ADM her PEP/LVET ratio increased by 0.13 above baseline (0.42) and her ejection fraction fell to 0.53; after a dose of 402 mg/m² her ejection fraction was 0.44. Her ECG voltage dropped by 34% from her pretherapy value. Using the "rigorous" or "nonrigorous" criteria described above, this patient's ADM therapy might have been discontinued after the first three courses of therapy.

Patient 2, a 7-year-old boy with Ewing's sarcoma, was treated with pulmonary radiation, cyclophosphamide, and ADM to a cumulative dose of 480 mg/m². This patient developed mild pulmonary edema while receiving iv fluids 3 1/2 months after his last dose of ADM. He has persistent evidence of a cardiomyopathy and is receiving digoxin and diuretics 9 months later. The patient did not have abnormal STIs at any time prior to the appearance of clinical CHF. His ECG voltage decreased by 30% of baseline after 360 mg/m² of ADM had been given, but this was less marked (31%) just before his final dose of ADM. The only test which was clearly abnormal was an echocardiogram obtained on the morning of his last scheduled dose of ADM; at that time his ejection fraction had fallen to 0.51. In contrast to patient 1, this patient's left ventricular function tests were never markedly abnormal. Cautious interpretation might have led to elimination of the last one or two doses of drug.

A similar contrast may be seen in patient 3, a 48-year-old man with mesothelioma, and patient 4, a 7-year-old child with acute lymphatic leukemia. Both of these patients had had prior responses to ADM and discontinuation of drug when cumulative doses of 400–500 mg/m² had been given. Seven and 24 months respectively after the last dose of ADM, the primary physicians felt that further ADM administration was justified because of progressive tumor refractory to other agents. Cardiac studies were obtained just before each additional drug dose; these are shown in figure 3. ADM was discontinued for the second time in patient 3 after a total dose of 760 mg/m². No clinical symptoms or signs had appeared, but the slow deterioration of PEP/LVET ratio and ejection fraction concerned the patient's oncologist. The patient is still followed regularly and has not had clinical evidence of CHF in 12 months of observation after the last dose of ADM.

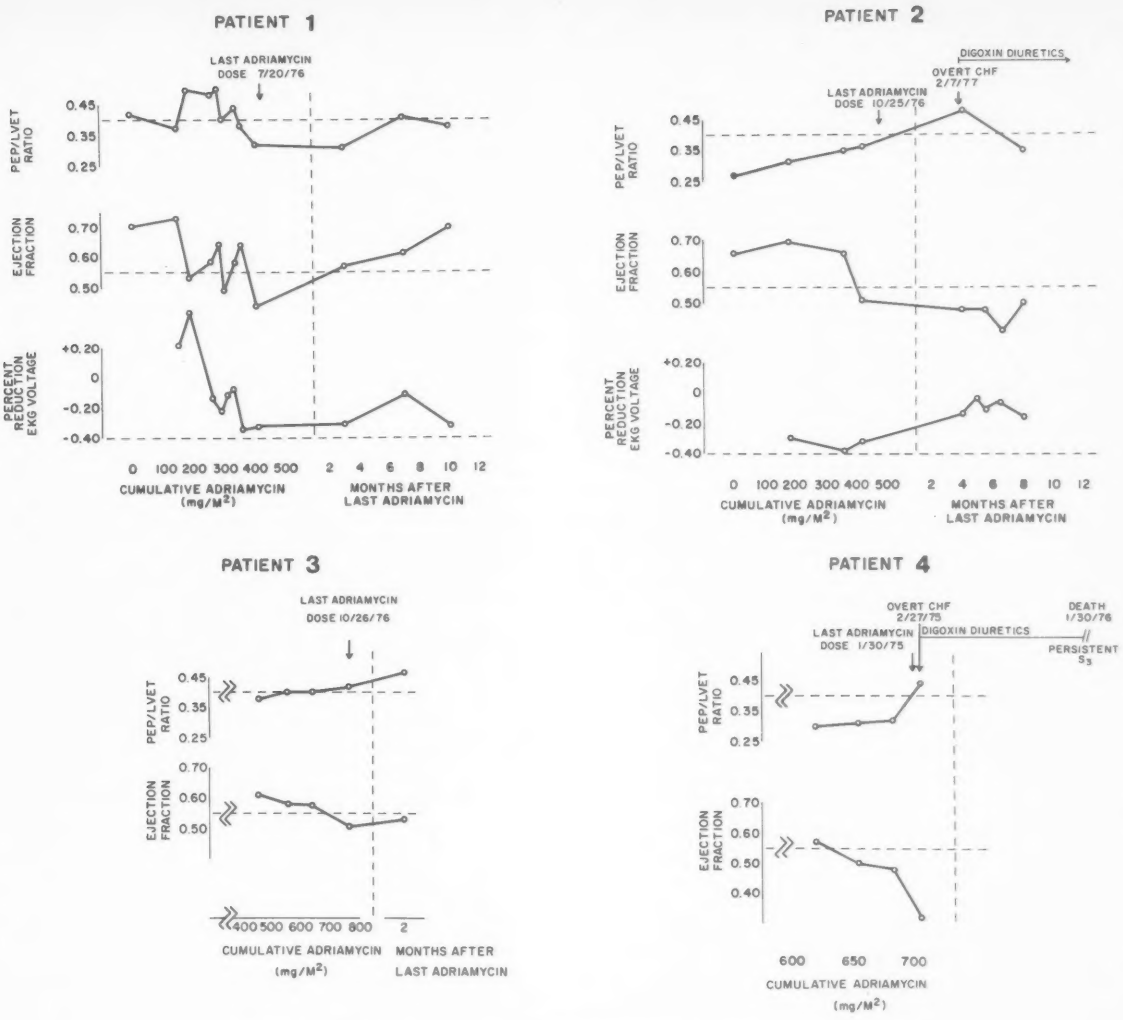

FIGURE 3.—ADM cardiomyopathy study: individual left ventricular function profiles.

Patient 4 was given a dose of 705 mg/m² without a change in STIs and with no single point of clear deterioration in the ejection fraction after the first dose. This patient went into frank pulmonary edema 3 weeks after the 705-mg/m² dose. Both of these patients had evidence of left ventricular compromise but the marked differences in their clinical courses were not predicted by the serial, noninvasive cardiac evaluations.

Noninvasive Testing as a Guide to Therapy

Transient abnormalities such as those observed in patient 1 were frequently noted. Because of this we have estimated the percentage of patients who would have had ADM discontinued before completion of a planned course if the left ventricular function studies had been used as a guide. The 103 patients who have completed therapy and have had at least two serial studies comprise the denominator for these estimates.

If the "rigorous" criteria had been used, 23 of these 103 patients might have had drug discontinued after a dose of 200–400 mg/m² had been given. These 23 patients now have a median followup of 10 months (range, 1–20) and no CHF has been observed in any of them. If "nonrigorous" criteria had been

applied, 32 of the 103 patients would not have completed their planned course. Median followup in these 32 patients is also 10 months (range, 0–32) and none have developed any signs or symptoms of CHF.

When the "rigorous" criteria developed for each of these tests were used, STIs were more frequently misleading than were ejection fractions or ECG voltage changes. However, transient abnormalities were often seen concomitantly in all three tests, and when "nonrigorous" criteria were used, there was little difference in the frequency of transient abnormalities in each of the tests. Among the very few patients who developed cardiomyopathy, there was no clear advantage of one or another of these tests in predicting CHF regardless of the criteria selected.

DISCUSSION

The mean PEP/LVET ratio rose and the mean ejection fraction fell as patients received higher cumulative doses of ADM. Even though the average values of the left ventricular function tests never departed from norms established for these tests, the mean values after 300–400 mg/m^2 of ADM had been given were significantly different from pretherapy results in the same group of patients. Thus, these studies seemed to reflect a slowly progressive deterioration of cardiac function which becomes detectable after doses of 300–400 mg/m^2 of ADM have been given.

In this analysis the incidence of cardiomyopathy was $< 2\%$. This is higher than the incidence among all patients included in phase II studies (1), but considerably lower than in some of the evaluations of noninvasive procedures in which the incidence of CHF ranged from 5% to 32% (3,7,8). The percentage of patients at each dosage level with detectable abnormalities of left ventricular function was also lower. In the first report on the use of STIs in evaluating patients receiving ADM, seven of eight patients given > 300 mg/m^2 had a PEP/LVET ratio > 0.40 (2); only 22% of the patients in this study with a total dose > 400 mg/m^2 had an increased ratio. An ejection fraction of < 0.43 was noted in six of the first 13 patients given > 400 mg/m^2 of ADM and studied with echocardiograms (3); only 10% of these patients given > 400 mg/m^2 had an ejection fraction of < 0.55. Finally, about 45% of all patients had an ECG voltage drop exceeding 30% in the original study relating ADM administration to changes in ECG voltage (8); 46% of these patients had a fall in ECG voltage of $> 30\%$, but only after > 400 mg/m^2 of ADM had been given.

The differences between the observations made in this study and those in previous reports may be due in large part to the manner of patient selection, since the patients entered in this protocol usually had a life expectancy > 2 years. Two groups of patients had no evidence of tumor at the time of initial study and were treated with adjuvant chemotherapy; leukemia patients were usually in complete remission prior to their first cardiac evaluation. Since there were no similar restrictions to entry in the protocols previously reported, it is likely that a large percentage of those patients had active disease and many may have been in terminal stages at the time of the last cardiac evaluation. Thus, it is likely that stress, such as anemia, cachexia, hypoxia, overhydration from iv fluid administration, acidosis, or fevers, may have influenced the results of previous studies.

This protocol was initiated in 1974. Since then it has become clear from animal studies (9) and from endomyocardial biopsies done in man (10) that (*a*) in spite of considerable heterogeneity in the severity of the damage, all hearts are affected by ADM at the dose schedules most frequently used, and (*b*) myocardial lesions may be progressive even after discontinuing drug therapy. Left ventricular function depends on both the intrinsic contractility of the myocardium *and* the stress placed on it. It is likely that there is a slowly progressive cell loss and a concomitant gradual decrease in the intrinsic contractility of all hearts treated with ADM. However, this process may be detected by noninvasive cardiac evaluation only when either (*a*) the damage is extensive enough to be manifest at rest, or (*b*) the patient is studied during a time of stress. It is possible that the transient changes observed do, in fact, reflect underlying heart damage and are seen intermittently only because of unappreciated variations in stress in such patients. Unless the external work load on the heart can be equalized for all heart studies, it may not be possible to quantitate and evaluate the degree of cardiotoxicity which has occurred in any one individual. Thus, even though the gradual attrition of cardiac reserve can be detected with these tests, it is not yet possible to predict which patients will develop clinically significant CHF or when this will occur.

ADM is currently one of the most valuable drugs available to the oncologist. It is our experience that patients who develop CHF, such as patients 2 and 4, can be successfully treated for long periods of time if clinical signs and symptoms are carefully observed and ADM is discontinued at the first suggestion of CHF. ADM has been used since 1974 at the Sidney Farber Cancer Institute as adjuvant therapy for both adult and pediatric patients at high

risk of recurrence; no patient receiving adjuvant treatment and otherwise free of disease has thus far developed CHF related to ADM. The cumulative dose limit of 450 mg/m^2 is usually observed unless the patient has progressive tumor responsive to anthracyclines and refractory to other drugs. Using previously published criteria, ADM would have been discontinued in 22% of these patients before this dose limit was reached. If the drug had been stopped whenever any test abnormality was noted, 31% of these patients would not have completed therapy. On the other hand, no more than one dose of drug would have been stopped in the few patients who did develop CHF, and it seems unlikely that this would have affected the course of these patients since the CHF was often very mild and treatable or reversible. Even among a few patients given a total dose of 600–800 mg/m^2, there were no easily recognized distinctions between those patients who eventually had clinical evidence of cardiomyopathy and those who did not.

We conclude that there is insufficient evidence at the present time to justify routine reliance upon STIs, ECG voltage changes, or echocardiographically determined ejection fractions to determine the optimal cumulative ADM dose in any individual patient. Repeated, careful, clinical examinations and dose limitations of about 500 mg/m^2 are still the simplest, least expensive, and most reliable guides to proper use of the anthracyclines.

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QRS Voltage Change With Adriamycin Administration

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SUMMARY

A decrease in the electrocardiographic limb lead QRS voltage of ≥ 30% was highly correlated with the development of congestive heart failure in patients treated with adriamycin (ADM). It is felt that if a decrease in limb lead QRS voltage ≥ 30% were detected in a patient receiving ADM, cardiomyopathy might be avoided or ameliorated by discontinuation of the drug.

[Cancer Treat Rep 62:931–934, 1978]

Adriamycin (ADM) can produce severe, disabling, and frequently fatal cardiomyopathy (1). At present, a cumulative dose limitation of 550 mg/m² is recommended to reduce the frequency of this complication (1). Despite this, some patients will develop cardiotoxic reactions at lower cumulative doses and others can tolerate doses much > 550 mg/m² without cardiotoxic effects (2). It is very disheartening to see a responding patient relapse shortly after discontinuing ADM at the present dose limitation, when it is possible that the patient might have safely tolerated additional doses of ADM. It is hoped that with some test or combination of tests a degree of cardiotoxicity can be detected which will allow the oncologist to more accurately administer ADM. Ideally, the tests should be safe, easy to perform, involve little patient inconvenience, and be specific without being too sensitive. Tests which are too sensitive detect the existence of cardiac damage without being able to predict if a patient is likely to develop symptomatic cardiomyopathy.

Tests currently under investigation include QRS voltage (3), systolic time interval (4), echocardiogram (5), QK_d interval (6), endomyocardial biopsy,[4] and isotope angiography.[5] In this study we evaluated various characteristics of patients treated with ADM, including low QRS voltage.

MATERIALS AND METHODS

The charts of 809 patients who received ADM between 1970 and 1974 at the M. D. Anderson Hospital and Tumor Institute were reviewed. Four hundred and thirty-nine patients received ADM alone and 370 received ADM in combination with cyclophosphamide. Seventeen patients experienced ADM cardiomyopathy and had electrocardiograms (ECGs) taken before the first dose of ADM and after the development of congestive heart failure (CHF). An additional 36 patients who did not show evidence of cardiotoxic effects and survived for at least 5 months after receiving > 400 mg/m² were selected for comparative evaluation. These patients also had ECGs taken before receiving ADM and at least 3 weeks after the last dose of ADM.

Most patients received ADM as a rapid iv infusion of 25–105 mg/m² every 3–4 weeks. Two patients received ADM for 3 consecutive days every 3–4 weeks; one developed CHF and the other did not.

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Five patients had daunorubicin substituted for ADM for one to three doses; two developed CHF and three did not. The dose of anthracycline administered was calculated as two thirds the dose of daunorubicin.

Figure 1 shows the method of calculating QRS voltage. ECGs were recorded with a 10-mm standard. The absolute deflection of QRS in the six limb leads was measured in millimeters from the lowest negative deflection to the highest positive deflection even if there was more than one deflection in a direction. The sum of the QRS voltages of the six limb leads in millimeters was calculated for each tracing, and the percent change in the sum of the QRS voltage was calculated from the pre-ADM ECG to the ECG obtained at the onset of CHF or the ECG with the lowest voltage after the last dose of ADM in patients who did not develop CHF. The limb leads were used because of the prominent changes observed in these leads and because of the variability of the QRS voltage in the precordial leads.

RESULTS

The characteristics considered in this study were sex, age, total dose of ADM in mg/m², days of ADM administration, dose of ADM per unit of time (mg/m²/day), percent change in QRS voltage, concurrent cyclophosphamide, and prior mediastinal radiation (table 1). Comparisons were made between patients with and without CHF with respect to these individual characteristics.

The only significant characteristic was percent change in QRS voltage. Patients with ADM cardiomyopathy had a much greater percent decrease in limb lead QRS voltage than patients who did not develop CHF. Figure 2 shows the distribution of the percent decrease in QRS voltage between the two groups of patients. The difference between the groups is highly significant ($P = 0.002$).

Sixteen of the 17 patients with cardiomyopathy

TABLE 1.—ADM cardiac toxicity: patient characteristics

Characteristic	Without CHF	With CHF
Sex		
Men	17	6
Women	19	11
Median (range)—		
Age in yrs	47 (15–74)	51 (20–69)
Total dose in mg/m²	510 (405–600)	510 (310–825)
Days of ADM administration	191 (129–433)	217 (120–489)
mg/m²/day of ADM	2.51 (1.30–4.53)	2.37 (0.94–4.66)
% change in QRS	–12 (+43 to –44)	–53 (–27 to –79)
No. of patients with—		
Concurrent cyclophosphamide	17	7
Prior radiotherapy	9	5

FIGURE 1.—Method of calculating QRS voltage.

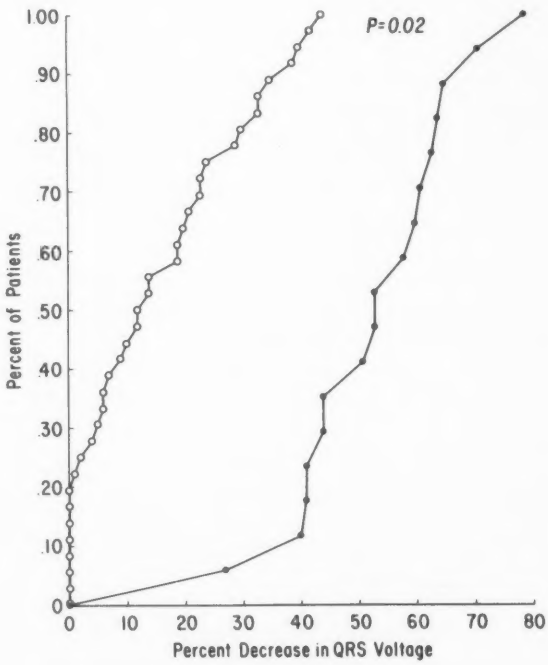

FIGURE 2.—Distribution of % decrease in QRS voltage for 17 patients with CHF (●) and 37 patients without CHF (○).

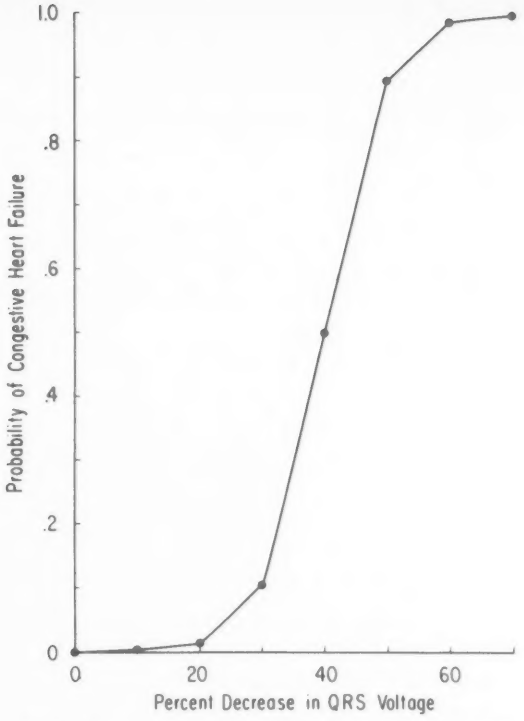

FIGURE 3.—Predicted probability of CHF by decreased QRS voltage.

had a ≥ 30% decrease in the sum of the limb lead QRS voltage. In six patients, an ECG was not obtained before the last several doses of ADM. Cardiomyopathy caused death in three of these inadequately followed patients. This reinforces the point that all patients receiving ADM must be evaluated carefully before each dose of ADM. In five patients, the sum of the QRS voltage in the ECG performed just before the administration of the last dose of ADM did not show a decrease in voltage of ≥ 30%. ADM was discontinued in these patients as they had reached a cumulative dose of approximately 550 mg/m² and were not candidates for additional ADM. None of these five patients died from cardiomyopathy. In the remaining six patients with cardiomyopathy, the ECG performed just before the last dose of ADM showed a ≥ 30% decrease in QRS voltage (range 44%–79%, median 61%). CHF caused death in two of these patients. Of the 36 patients who did not develop CHF, only eight had a decrease of ≥ 30%, and six of these had received larger cumulative doses of ADM than are currently recommended. Most of the eight patients who had a ≥ 30% decrease in QRS voltage died from progressive disease; none developed CHF. A chi-square test showed that a ≥ 30% decrease in QRS voltage was significantly correlated with the presence of CHF ($P < 0.001$).

A stepwise linear logistic regression procedure (7) was used to determine the relative importance of each characteristic in predicting the development of CHF. A regression equation was obtained. The only significant characteristic was percent decrease in QRS voltage ($P < 0.01$). The other characteristics were not nearly as significant. For example, total dose, which from all previous work would be expected to be significantly related to the development of CHF, was selected as the second most important characteristic; however, the importance was not significant ($P = 0.17$), probably because patients with low cumulative doses were excluded from analysis.

A test of the goodness of fit of the regression equation to the observed data is shown in table 2. The predictive probabilities were grouped into intervals and the number of patients with CHF in each interval was observed. There is a very close relationship between the observed and predicted number of patients having CHF. This indicates that percent decrease in QRS voltage can separate patients into groups that have differing probabilities of CHF.

Figure 3 shows the predictive probability of CHF plotted against the percent decrease in QRS voltage. The risk of CHF increased sharply from 0.10 to 0.90 at decreases in QRS voltage between 30% and 50%.

DISCUSSION

A decrease in the limb lead QRS voltage of ≥ 30% was the most important difference between the patients who developed CHF and those who did not.

Low QRS voltage has been noted in other situations such as hypothyroidism, Addison's disease, pericardial effusion, other cardiomyopathies, and chronic pulmonary disease, but not in CHF. Pericar-

TABLE 2.—Test of goodness of fit—comparison of observed and predicted probability of CHF

Predicted probability* of CHF (range)	No. of patients		
	Total	Observed with CHF (%)	Predicted with CHF
0–0.19	32	1 (3)	0.761
0.20–0.39	1	0	0.253
0.40–0.59	5	3 (60)	2.545
0.60–0.79	4	2 (50)	2.707
0.80–1.00	11	11 (100)	10.733

*Chi-square statistic is 0.601 for 4° of freedom, $P = 0.963$.

dial effusion is not a common finding in autopsies of patients dying of ADM cardiomyopathy (8). We therefore feel that low QRS voltage is primarily a reflection of the cardiomyopathic process. Serial endomyocardial biopsies of patients receiving ADM at various dose levels taken after completion of ADM administration demonstrate progressive loss of myocardial cells continuing for at least 2 years after the last dose (*see* footnote 4). It appears that every dose of ADM causes some degree of cardiac damage with only a few patients developing symptomatic cardiomyopathy. There seems to be a critical loss of myocardial cells for each individual before CHF develops and this loss of myocardial cells is reflected by a decrease in ECG QRS voltage.

We believe that if a decrease in QRS voltage of $\geq 30\%$ were detected during the course of ADM therapy, symptomatic cardiomyopathy might be avoided or ameliorated by discontinuation of ADM in these high-risk patients. CHF may still develop because the decrease in QRS voltage may not precede CHF by a sufficient interval to prevent its development by early discontinuation of ADM.

To further reduce the frequency of cardiomyopathy, it will be necessary to develop a method of antagonizing the cardiotoxic action of ADM, with such recently postulated agents as α-tocopherol (9) or coenzyme Q_{10} (10), or to develop an ADM analog which is not cardiotoxic (11).

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Cardiac Toxicity of Adriamycin-DNA Complex and Rubidazone: Evaluation by Electrocardiogram and Endomyocardial Biopsy[1]

Robert S. Benjamin,[2,3,*] Jay W. Mason,[3] and Margaret E. Billingham[3]

Long-term use of adriamycin (ADM) and daunorubicin has been limited by the development of severe, dose-dependent cardiomyopathy (1–3). Since cardiomyopathy from ADM is uncommon below a cumulative dose of 500–550 mg/m², dose limitation has been the most widely practiced method of avoiding cardiac toxicity. Systolic time intervals have been used to detect anthracycline-induced cardiomyopathy but may be both too sensitive to indicate the need for discontinuation of treatment and too insensitive to predict impending congestive heart failure (CHF) (4,5). More recently, we have described a good correlation between anthracycline-induced CHF and a fall in the sum of the QRS voltage in the six limb leads on electrocardiograms (ECG) following ADM therapy > 30% compared with the pretreatment value (6).

The most direct method of evaluating myocardial damage from anthracyclines is endomyocardial biopsy. The degree of damage can be assessed semiquantitatively according to the method of Billingham et al (7) in which a grade 1 change reflects minimal damage, a grade 2 change reflects moderate damage, and a grade 3 change reflects severe damage. The degree of myocardial damage correlates extremely well with cumulative ADM doses with a mean score of 2 for patients receiving > 500 mg/m² (8).

One approach to prevention or diminution of anthracycline-induced cardiomyopathy is the development of analogs which retain antitumor effect but show less cardiac toxicity per unit time when administered at equitoxic doses. We have tested two such analogs, ADM-DNA complex and rubidazone (9,10). This report describes our evaluation of the cardiac toxicity of those two agents.

MATERIALS AND METHODS

Patients undergoing therapy with ADM-DNA complex or rubidazone were studied with serial measurement of QRS voltage on ECG according to the procedure of Minow et al (6). In addition, clinical evaluation of CHF was performed, and patients treated with ADM-DNA complex were limited to a cumulative dose of 750 mg/m². Endomyocardial biopsy was performed in three patients treated with ADM-DNA complex after cumulative doses of 625, 555, and 520 mg/m² of ADM of which 475, 555, and 310 mg/m² were given in the form of ADM-DNA complex and the remainder as free ADM prior to initiation of ADM-DNA therapy. Altogether, 58 patients received ADM-DNA of whom 23 had received prior ADM. One hundred and twenty-seven patients received treatment with rubidazone. Cardiac biopsy was obtained in two patients at cumulative rubidazone doses of 1550 mg/m² (in a patient without prior anthracycline therapy) and 950 mg/m² (in a patient previously treated with 150 mg/m² of ADM).

RESULTS

ADM-DNA Complex

Of the 58 patients treated with ADM-DNA complex, 11 demonstrated some clinical cardiac abnormality: nine had a QRS voltage fall > 30%, one had unexplained cardiomegaly at autopsy, and one had CHF with a QRS voltage fall of 28%. Five of the nine patients with a QRS voltage fall > 30% had no prior anthracycline therapy and had received cumulative ADM-DNA doses of 240–450 mg/m². Four patients in this study developed CHF. Extensive prior anthracycline therapy together with leukemic infiltration of the heart in one patient and underlying heart disease in a second patient seemed to be the most likely causes for CHF. In a third patient, prior anthracycline therapy contributed only partially and the fourth patient developed CHF clearly

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TABLE 1.—Rubidazone cardiomyopathy

Patient No.	Cumulative dose (mg/m²)			Risk factors	ECG warning	Approximate contamination (% daunorubicin in rubidazone)
	Rubidazone	Prior ADM	Prior daunorubicin			
1	2600	270	—	—	38% QRS voltage decrease at 2050 mg/m²	10
2	1750	135	—	Hypertension	Not done	10
3	2000	—	340	—	43% QRS voltage decrease	10
4	1280	—	385	Radiation therapy	27% QRS voltage decrease	30
5	1110*	210	—	Abnormal ECG	None	30
6	1050*	120	—	—	Not done	30
7	1310	100	—	—	40% QRS voltage decrease	30

*Probable cardiomyopathy, but not well documented.

due to ADM-DNA at a dose of 475 mg/m² following 150 mg/m² of free ADM, with grade 3 changes on endomyocardial biopsy (fig 1).

Both patients treated with ADM-DNA exhibited cellular changes similar to those previously described for ADM alone: loss of contractile elements (figs 1 and 2), swelling of sarcoplasmic reticulum, and/or vacuolization. In the one patient who had also received previous ADM, the changes were so severe and diffuse in biopsies from both the left and right ventricles that a pathologic score of grade 3 (the highest) was given.

Rubidazone

Cardiac toxicity manifested by CHF was seen in seven patients treated with rubidazone and was fatal in six. These were all patients with acute leukemia and prior anthracycline therapy treated with rubidazone as a single agent to re-induce complete remission after leukemic relapse. Cumulative doses ranged from 1050 to 2600 mg/m² after 100–270 mg/m² of ADM or 340–385 mg/m² of daunorubicin (table 1). The initial three patients demonstrated cardiac toxicity at doses between 1750 and 2600 mg/m². At that time and currently, the rubidazone used contained approximately 10% contamination with daunorubicin. In contrast, four patients treated just before the expiration of a batch of rubidazone which was found to have approximately 30% daunorubicin contamination developed cardiac toxicity at doses between 1050 and 1310 mg/m². Four of five patients who had an ECG prior to the last dose of rubidazone showed QRS voltage decreases of 27%–43% (three patients > 30%). One patient showed no fall in QRS voltage prior to development of CHF (table 1).

Both patients biopsied after rubidazone also showed myocyte damage similar to that described for ADM alone. The one patient who received rubidazone only showed cells with loss of contractile elements as well as myocytes with vascular degeneration (fig 3). In addition, it is interesting to note that in both of the patients receiving rubidazone there was a definite aggregation of sarcoplasmic vacuoles around the intercalated disc.

DISCUSSION

Prior to the use of endomyocardial biopsy in our studies, we were faced with an interesting dilemma. The question of cardiac toxicity was a phase I question but one which could only be answered in the presence of a positive phase II clinical trial where patients had the opportunity to receive enough drug to develop cardiac toxicity. Both ADM-DNA and rubidazone proved to be active agents, the former similar to ADM in activity and other toxicity, and the latter highly effective in the treatment of acute leukemia (9,10). Although ECG voltage tended to fall prior to the development of CHF with rubidazone, a 30% voltage decrease was not seen in two patients who developed CHF. Although prior anthracycline therapy confuses the issue, our best current estimate of the cardiotoxic dose of rubidazone is 1500 mg/m² based on the grade 2

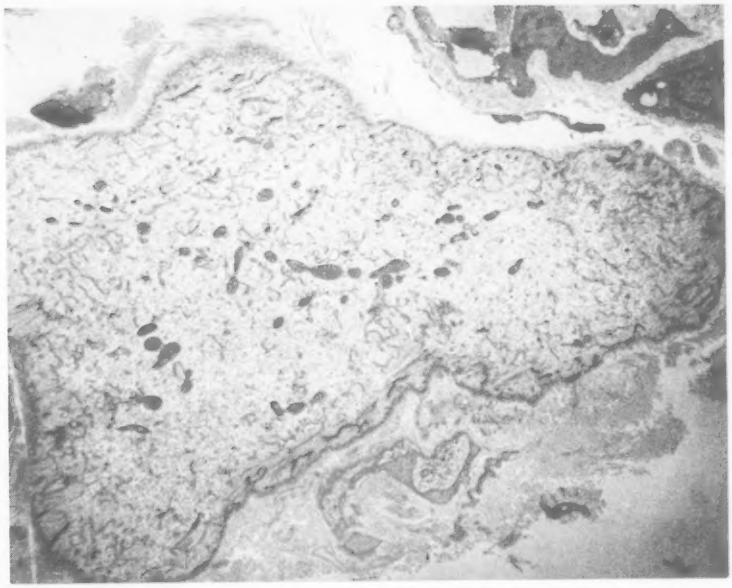

FIGURE 1.—Endomyocardial biopsy tissue demonstrating a myocyte almost completely devoid of contractile elements and organelles. Similar changes were seen in endomyocardial biopsies of both left and right ventricles (magnification, × 5750).

FIGURE 2.—Endomyocardial biopsy tissue showing a myocyte with loss of myofibrils (↓) compared with an adjacent unaffected myocyte (↓↓) (magnification, × 5750).

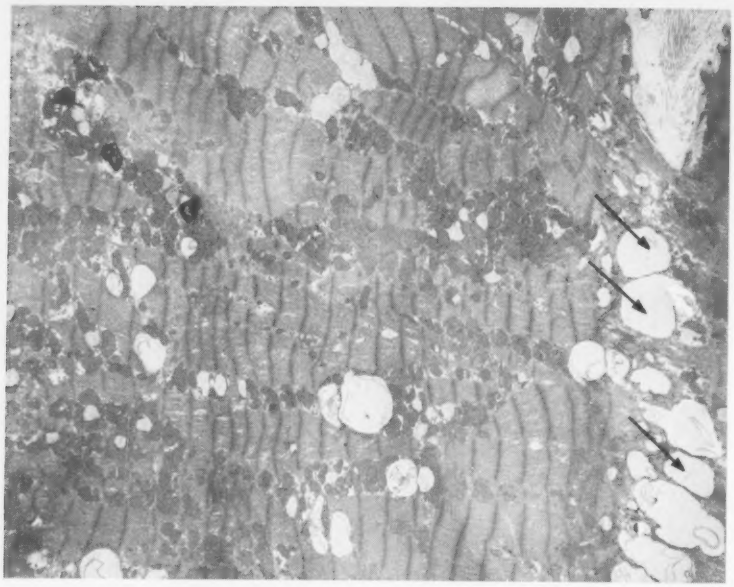

FIGURE 3.—Endomyocardial biopsy tissue from rubidazone-treated patient showing vascuolization of sarcoplasmic reticulum (↓) aggregated particularly along the intercalated discs (magnification, × 5750).

lesion in our single patient at that level without prior anthracyclines.

ADM-DNA complex was designed as a noncardiotoxic ADM. Our data indicate that at least in our preparation, the material behaved like free ADM with regard to efficacy, acute toxicity, and cardiac toxicity. When our first patient was biopsied 11 months after receiving a total of 625 mg/m^2 (475 mg/m^2 of the DNA complex and 150 mg/m^2 of free ADM), because of the development of atypical right-sided CHF, we did not strongly suspect ADM cardiomyopathy. The biopsy was so striking in its abnormality (fig 1) that there was little question as to the diagnosis. Although we were convinced of the cardiac toxicity of the complex after that result, the relative contribution of the first dose of 150 mg/m^2 of free ADM was not resolved, and we were unwilling to give our next patient > 550 mg/m^2 in the absence of prior anthracyclines without a biopsy. His biopsy (fig 2) showed changes equivalent to those which might be expected from a similar ADM dose (9). Although we prepared our ADM-DNA complex precisely according to the method of Trouet et al (11), intrinsic viscosity of our DNA solution was somewhat reduced compared to that of Trouet's. It is felt possible, therefore, that the difference between our results and those of European investigators who have not found ADM-DNA complex to be cardiotoxic may be explained in part by denaturation of the DNA solution in our complex prior to its use.

Endomyocardial biopsy has allowed us to determine the relative cardiac toxicity of various analogs of ADM quickly and simply in patients who are asymptomatic, long before the development of CHF. Since grade 1 changes are noted even after as little as 100–200 mg/m^2 of ADM, this technique offers for the first time a reliable test of the comparative cardiac toxicity of the anthracyclines at safe cumulative doses.

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Radionuclide Angiography for the Evaluation of Anthracycline Therapy [1]

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SUMMARY

A sensitive and reproducible method to noninvasively monitor cardiac function in patients receiving anthracycline therapy is badly needed. The radionuclide ejection fraction (EFrn) appears to be a suitable technique to provide this hemodynamic information. This paper describes the technique for determining the left ventricular EFrn with the use of technetium^{99m}-labeled rbcs, a gamma scintillation camera, and a dedicated computer. The comparison of radionuclide and radiographic contrast EFrn showed a high correlation (r = 0.84) in 30 patients.

[Cancer Treat Rep 62:941–943, 1978]

The cardiac toxicity resulting from anthracycline therapy is a major factor in limiting the use of these drugs. Reliable, noninvasive methods to quantitate the severity of cardiac dysfunction resulting from the use of these agents are needed. It is hoped that with the availability of a sensitive and reliable technique to monitor cardiac toxicity, it will be possible to safely give larger total doses of these drugs in order to obtain a greater therapeutic effect. The radionuclide ejection fraction (EFrn) technique holds great promise of being such a method because it noninvasively determines one of the most reliable measures of cardiac function—the left ventricular EF. This paper will describe the radionuclide technique used for measuring the EFrn at the University of Washington affiliated hospitals.

Radioisotope angiography can be carried out by either the first-transit or the blood-pool equilibrium technique (1,2). The blood-pool technique allows repeated observations of EFrn over several hours and is, therefore, useful for observing changes in left ventricular performance in response to drug or other interventions. Blood-pool scans are usually carried out with either labeled albumin or rbcs. Technetium^{99m}-labeled rbcs maintain a higher percent of the radioisotope activity in the intervascular compartment and are, therefore, preferable for radioisotope angiography.

DESCRIPTION OF PROCEDURE

After a full explanation of the procedure to the patient, a 21-gauge intercath is placed in an arm vein and 6 ml of blood is withdrawn. The sample is spun down, the rbcs are labeled with technetium^{99m} with the use of the Smith and Richards kit (3), and 25 millicuries of technetium^{99m}-labeled rbcs (about 2 ml) is reinjected into the patient through the venous intercath. After allowing 5 minutes for equilibrium, the patient is connected to the ECG Brattle gate with appropriate electrodes and imaged with a gamma scintillation camera in the anteroposterior and 45° left anterior oblique (LAO) positions. The scintillation camera is fitted with a high-resolution parallel-hole collimator, and the energy window is set at 20% and centered at 140 KEV. The gamma scintillation data are collected in the computer so that each 40-msec segment of the cardiac cycle is stored in a separate section of computer core memory and may be retrieved as a separate image. Collection is carried out until each 40-msec image contains 300,000 counts. With current acquisition rates, this requires from 5 to 8 minutes of imaging time for each view.

Using the end-diastolic image in the LAO view, the area of left ventricular activity and an appropriate background region are selected. Time-activity

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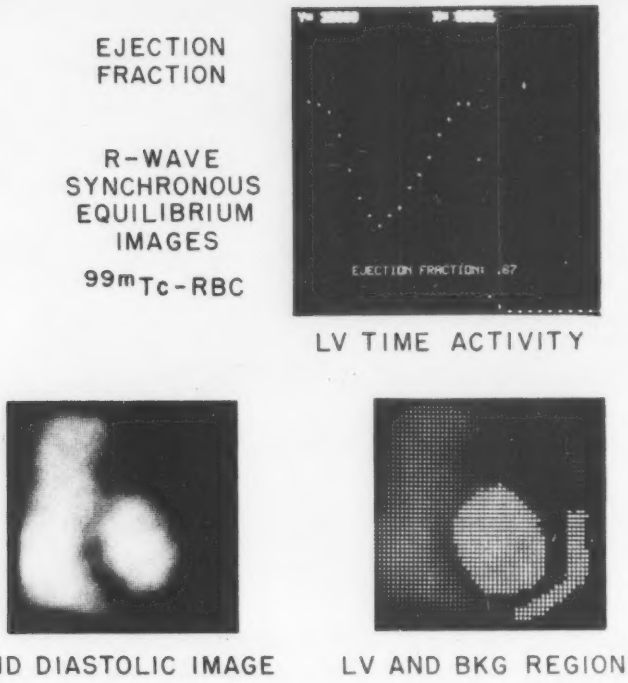

FIGURE 1.—Gated equilibrium blood-pool time-activity method. The 45° LAO image of the heart at end-diastole is shown on the lower left. On the lower right, left ventricular and background regions of interest have been defined by light pen. The upper plate displays the synchronized composite time-activity curve generated from the background-subtracted left ventricular region of interest during several hundred cardiac cycles.

curves are then constructed from the left ventricular region and corrected by subtraction of background activity as illustrated in figure 1. From the corrected time-activity curve, the EFrn is determined as:

$$\text{EFrn} = \frac{\text{end-diastolic counts} - \text{end-systolic counts}}{\text{end-diastolic counts}}.$$

The EFrn determined by this technique compared well with the EF determined by X-ray contrast cineangiograms in 30 patients with various types of heart disease, as shown in figure 2 (4). There is better agreement between these two techniques when the EFrn is reduced below the normal limit of 50%. Two measurements of EFrn have been carried out several days apart in 36 patients by Weaver et al,[3] and have shown a close correlation ($r = 0.92$). The 40-msec images obtained from these gated blood-pool scans may also be displayed on a television monitor as repetitive images of the one recorded cardiac cycle, simulating a cineangiocardiogram. This cine format allows the observer to evaluate all four cardiac chambers and, in the LAO view, gives an excellent display of both right and left ventricular contraction and interventricular septal thickening. In patients with ischemic heart disease, left ventricular segmental contraction abnormalities can also be observed.

DISCUSSION

The left ventricular EF has been extensively utilized in cardiology for about 10 years. This simple ratio of left ventricular stroke volume to end-diastolic volume, measured from a biplane or single-plane left ventricular cineangiogram, has correlated well with clinical syndromes of heart failure in various types of heart disease (5–7), and has been shown to be a useful predictor of surgical risk and of long-term survival in medically and surgically treated cardiac patients (8,9). For these reasons, the

[3]Weaver WD, Williams DL, Hamilton GW, et al. The first-transit radionuclide ejection fraction: a study of data analysis techniques, reproducibility, and correlation with the contrast angiogram. Submitted for publication. J Nucl Med.

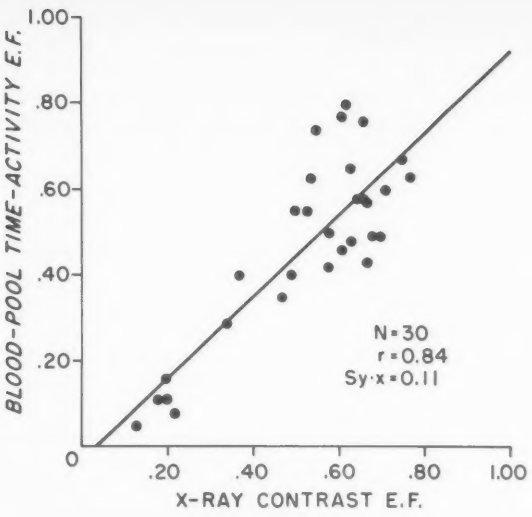

FIGURE 2.—Comparison of gated equilibrium blood-pool radionuclide EFrn with right anterior oblique X-ray contrast EFrn. Note that the agreement between the 2 methods is best for X-ray contrast EFrns < 0.55 (r = 0.96).

EFrn has become a measurement of left ventricular pump performance with which old and new indices of cardiac function are often compared.

Current noninvasive techniques to evaluate left ventricular function include systolic time intervals and the estimation of left ventricular EF from single-dimensional echocardiography. Both of these techniques have gained some popularity because they have often yielded results which have correlated with angiographically determined EF. Unfortunately, neither of these techniques, despite their appeal related to simplicity and cost, provides information which is as direct, reliable, and reproducible about left ventricular performance as the angiographic EF (10,11). The close correlation of the EFrn with the radiographic contrast EF and the visual display of right and left ventricular contraction make the radioisotope angiographic technique a major advance in the noninvasive evaluation of cardiac performance.

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Time- and Dose-Dependent Changes in Ejection Fraction Determined by Radionuclide Angiography After Anthracycline Therapy[1]

J. W. Singer,* K. A. Narahara, J. L. Ritchie, G. W. Hamilton, and J. W. Kennedy[2]

SUMMARY

Twenty patients receiving anthracycline chemotherapy were studied by the technique of radionuclide ejection fraction (EFrn). This technique is capable of detecting noninvasively small changes in left ventricular function. Two patterns of anthracycline toxicity emerged: (*a*) an acute toxicity observable between 24 and 72 hours after administration of > 60 mg/m² of anthracycline with some recovery noted by 72–96 hours (no changes were observed within the first 4 hours after administration of the drug), and (*b*) a chronic dose-dependent decrease in left ventricular function when studies were performed 3 weeks after the last dose of anthracycline. After anthracyclines were stopped, four of four patients showed significant recovery in left ventricular function. We concluded that the radionuclide EFrn is a sensitive noninvasive index of left ventricular function which can be used to serially study patients receiving anthracycline therapy and can potentially be used to evaluate pharmacologic means for preventing anthracycline cardiotoxicity.

[Cancer Treat Rep 62:945–948, 1978]

We have used the technique of ejection fraction (EFrn) determined by radionuclide angiography, as described in the companion paper by Dr. J. W. Kennedy, to study resting cardiac function in patients receiving short- and long-term anthracycline therapy. We studied the acute as well as the chronic effects of anthracyclines on left ventricular function since radionuclide angiography appeared to be far more sensitive than other techniques for assessing cardiac damage secondary to anthracycline therapy. For the acute studies, EFrn's were determined at 0, 5, 10, 60, and 240 minutes, 24 and 72 hours, and 1 and 3 weeks after single or multiple doses of adriamycin (ADM) or daunorubicin. For studies of chronic anthracycline toxicity, we attempted to study patients before any anthracycline therapy had been given and then 3–4 weeks after their last dose of anthracycline at cumulative doses of > 250 mg/m². Four patients who had marked decreases in EFrn's during the chronic evaluations were re-studied between 6 and 14 weeks after stopping anthracycline therapy to determine whether significant recovery occurred.

CHRONIC ANTHRACYCLINE CARDIOTOXICITY

Table 1 contains the age, diagnosis, and therapy of the patients studied. Figure 1 illustrates the relationship between cumulative doses of anthracycline and EFrn determined either 3 or 4 weeks following the indicated dosage. Each data point represents a single study on a single patient. The points that are connected show an individual patient's progression as the cumulative anthracycline dose increased. For the purpose of this figure, ADM and daunorubicin doses have been considered as equally cardiotoxic due to the small patient population. It is evident that at any level of cumulative anthracycline dose, there is an inverse correlation between that dose and the EFrn. The *P* value of the correlation coefficient showed it to be significant at the 1% level. If a lower limit of normal for the EFrn of 0.51 is set, 12 of the 15 patients studied had abnormal EFrn's after receiving cumulative anthracycline doses ranging between 100 and 600 mg/m². At cumulative doses > 450 mg/m², EFrn's were significantly below normal in four of five patients and ranged from 0.19 to 0.37.

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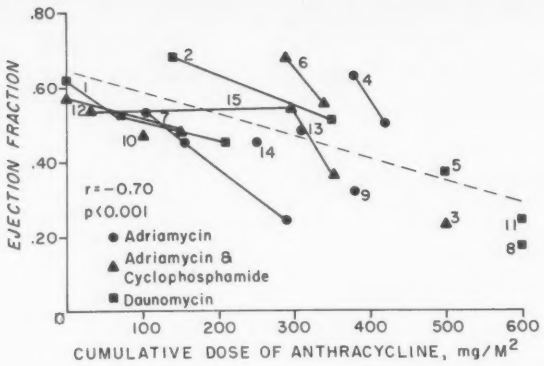

FIGURE 1.—Relationship between EFrn and cumulative dose of anthracycline. EFrn determinations were obtained at control or 3–4 wks after anthracycline administration. Solid connecting lines = serial measurements in the same patient; broken line = the least-squares fit ($r = 0.07$; $P < 0.001$) for all data points.

In only one of these patients were there symptoms or physical findings consistent with significant cardiac dysfunction. Patient 8, at a total dose of 600 mg/m² of daunorubicin, had moderately decreased exercise tolerance with no obvious congestive heart failure (CHF). He relapsed shortly after this study was done and during attempted re-induction chemotherapy with further daunorubicin went into CHF and died.

One of our serially studied patients had a correlative clinical parameter which suggested incipient anthracycline cardiotoxicity; he was a 64-year-old man with metastatic breast cancer (patient 7) who received a total dose of 340 mg/m² of ADM given at 3-week intervals in combination with cyclophosphamide. A routine electrocardiogram (ECG) demonstrated a 50% decrease in QRS voltage when compared to his previous ECG taken before starting anthracycline therapy. The EFrn showed a fall from 0.68 to 0.53. Drug therapy with ADM was halted in view of the voltage decline as has been advocated by others (1). Five weeks later the EFrn had returned to 0.65 and the ECG voltage was back to normal.

We re-studied three other patients who had received high doses of anthracyclines at various time intervals after the drugs were stopped to determine the potential reversibility of the abnormal EFrn's. The cumulative doses for each of the four patients when the drug was stopped are shown in figure 2, with the initial EFrn's 3–4 weeks after the last anthracycline dose and 13–25 weeks later. The average EFrn rise for the three patients was from a mean of 0.32 ± 7.6 to 0.55 ± 10.8 (SD). Differences between these values are significant at the 5% level (Wilcoxon rank-order test).

TABLE 1.—Clinical data in patients receiving anthracyclines

Patient No.	Age (yrs)/sex	Diagnosis	Primary drug therapy	Other potentially cardiotoxic therapy
1	64/M	Acute myelocytic leukemia	Daunorubicin	
2	27/M	Acute myelocytic leukemia	Daunorubicin	
3	49/M	Acute myelocytic leukemia	Daunorubicin	
4	53/M	Giant cell carcinoma, lung	ADM	Cyclophosphamide
5	54/F	Carcinoma, breast	ADM	
6	28/M	Acute myelocytic leukemia	Daunorubicin	
7	64/M	Carcinoma, breast	ADM	Cyclophosphamide
8	82/M	Myeloma	ADM	
9	68/M	Oat cell carcinoma, lung	ADM	
10	22/M	Carcinoma, maxillary sinus	ADM	Cyclophosphamide
11	21/M	Acute myelocytic leukemia	Daunorubicin	
12	60/M	Nodular poorly differentiated lymphoma	ADM	Cyclophosphamide
13	67/M	Oat cell carcinoma, lung	ADM	4000 rads to mediastinum
14	59/M	Myeloma	ADM	
15	63/F	Carcinoma, breast	ADM	Cyclophosphamide
16	21/M	Acute myelocytic leukemia	Daunorubicin	

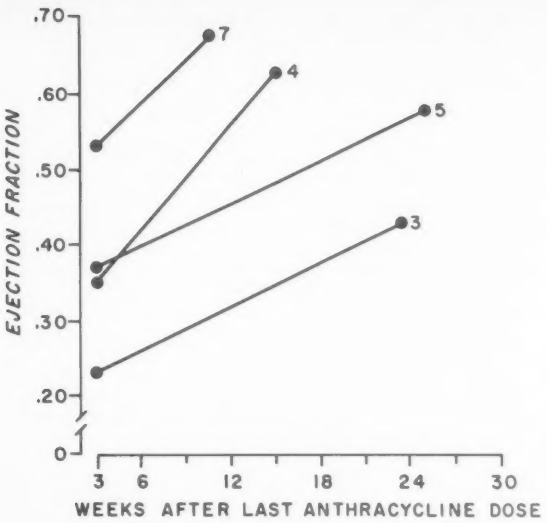

FIGURE 2.—Improvement of EFrn in patients receiving large cumulative doses of anthracycline (patients 4, 5, and 6). The low EFrn (average, 0.32) at the termination of anthracycline therapy rose to an average of 0.55 in the 14–24 wks after drug therapy was terminated.

ACUTE ANTHRACYCLINE CARDIOTOXICITY

When patients receiving anthracycline therapy were studied serially, before, within 4 hours of receiving the drug, and several times afterward over the following week, a different pattern of toxicity emerged. We have currently studied eight patients receiving doses of anthracycline between 20 mg/m² × 1 and 70 mg/m² × 3 for acute changes in EFrn. Our patients had previous anthracycline doses between 0 and 500 mg/m². Five patients were studied at 0, 5, 10, 60, and 240 minutes after anthracycline. No patient had any change in EFrn within the first 4 hours after the drug was administered. However, five of eight patients receiving doses ≥ 60 mg/m² showed moderate to severe drops in EFrn at 24 hours. The most extreme example is shown in figure 3. This 62-year-old woman with metastatic breast cancer had received a dose of 500 mg/m² of ADM with a good clinical response and no evidence of cardiotoxicity, either clinically or on chronic EFrn studies when the drug was stopped. She received cyclophosphamide, methotrexate, and 5-fluorouracil, but after 4 months she developed generalized progressive breast cancer. She was again started on ADM and the acute studies shown in figure 3 were performed before and after she received an additional dose of 60 mg/m². At 24 hours a marked drop in the EFrn was noted which was not accompanied

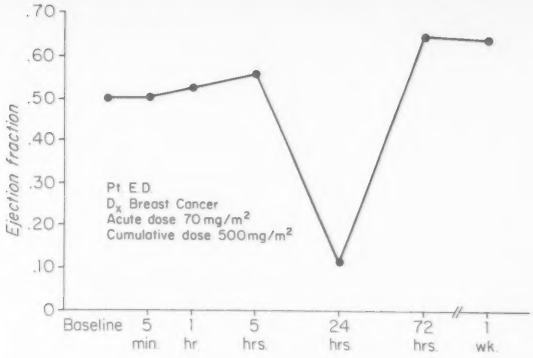

FIGURE 3.—The EFrn during an acute toxicity study on a 62-yr-old woman with metastatic breast cancer. No changes were noted in her baseline EFrn of 0.51 until 24 hrs when it dropped to 0.14. At 72 hrs the EFrn had returned to normal (0.62).

by any clinical evidence of CHF. Complete recovery was noted by 72 hours. We have not seen a drop this dramatic in any other acute studies. This was, however, the only acute study we performed on a patient with such a high cumulative total dose. The three studies we performed in which there was no decline in EFrn at 24–72 hours were performed on patients receiving 30–60 mg/m² of ADM at lower cumulative doses.

The acute physiologic changes detectable by EFrn may correlate with the histologic changes described by Jaenke (2) in rabbits receiving anthracycline in doses of 10–20 mg/kg and by Lambertenghi-Deliliers et al (3) in mice at a dose of 10 mg/kg. They observed changes in cell nuclei within 20 minutes and mitochondrial damage within 14 hours. One to three days later they noted changes in myofibrillar processes which might lead to observable changes in contractile efficiency.

Anthracyclines are thought to cause cardiotoxicity by oxidation of membrane lipids and inhibition of oxidative phosphorylation (4,5) as well as by interfering with DNA synthesis (6). We would like to speculate that the decrease in EFrn we have noted in our acute studies is due at least partially to the former mechanism, whereas the inability of the heart to completely repair itself by hypertrophy while anthracycline therapy is continued is due to the latter. The return in EFrn towards normal following discontinuation of anthracycline might well be due to cardiac hypertrophy.

Analyses of the radionuclide images suggest that the end-systolic volume enlarges disproportionately to the end-diastolic volume as the overall EFrn falls. Thus, it is not unreasonable to expect that

early cardiac decompensation from anthracycline cardiotoxicity would not be associated with roentgenographic evidence of cardiomegaly. Rather, as the end-systolic volume increases, overall function measured by EFrn would fall until irreversible failure and rapid cardiomegaly ensue, as has been the case in several reports of lethal anthracycline toxicity.

We conclude that radionuclide EFrn's can noninvasively detect both acute and chronic anthracycline cardiotoxicity. The acute toxicity appears after 4 but within 24 hours after the drug is administered and some recovery is observed within 48–72 hours. Anthracycline chronic toxicity is dose-dependent even at low cumulative levels; however, it does appear to be at least partially reversible over a period of weeks following cessation of therapy. Our results also indicate that not all patients develop chronic anthracycline toxicity since we have serially studied two patients up to doses of 500 mg/m^2 in whom no chronic decrease in EFrn was noted. Our overall results suggest that the EFrn is a reliable, noninvasive means for following left ventricular function during the course of anthracycline therapy, and that the technique with further clinical studies may allow the safe administration of anthracycline in some patients to beyond the currently recommended doses. Radionuclide EFrn's may be a useful technique either for evaluating pharmacologic intervention with newer anthracycline congeners (7) and for evaluating conjoint therapy with agents thought to prevent cardiac toxicity (8).

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Noninvasive Assessment of Cardiac Dysfunction in the Cancer Patient

John S. Gottdiener [1,*]

SUMMARY

The concepts of left ventricular function are reviewed with an emphasis on the pitfalls in the clinical assessment of myocardial performance. The application of noninvasive cardiac diagnostic techniques is discussed, including physical examination, systolic time intervals with external pulse recordings, echocardiography, and radionuclide cineangiography.

[Cancer Treat Rep 62:949–953, 1978]

Patients with malignant disease are susceptible to cardiac dysfunction as a consequence of the disease itself or of its therapy. Because repeated cardiac assessment of these patients is often required, the application of diagnostic techniques which may be repeated frequently, without discomfort or risk to the patient, is of special interest.

Serial assessment of left ventricular function is particularly important in the patient receiving adriamycin (ADM), where clinical cardiomyopathy may occur unpredictably even after the drug is discontinued. It is important for the oncologist to appreciate both the uses and limitations of such modalities in helping to assess ventricular function as well as pericardial disease in the oncology patient.

There is controversy concerning the reliability of noninvasive cardiac diagnostic techniques vis à vis invasive procedures for the assessment of left ventricular function, including left ventriculography and high-fidelity pressure measurements during isovolumic systole. However, all techniques are limited by the difficulty of isolating, in the clinical context, the contractile properties of the myocardium from extrinsic factors which affect cardiac performance.

While the purpose of the heart is simply to pump blood at a sufficient rate to allow peripheral delivery of oxygen and removal of wastes, it may do so in circumstances where the left ventricular myocardium has been severely compromised, and may fail to do so despite the absence of intrinsic disease of the heart muscle.

Accordingly, measurement of cardiac output does not suffice to define cardiac function. Although oversimplified, left ventricular performance (fig 1) may be considered the sum of: (*a*) preload or resting muscle length; (*b*) afterload or impedance to the ejection of blood; and (*c*) the contractile state of the myocardium—referring to the intrinsic ability of the myocardium to generate force, independently of factors such as loading and catecholamines.

The various measures of left ventricular function (1) may be divided into two groups (fig 2).

Isovolumic phase indices of contractility describe cardiac performance from the onset of left ventricular pressure rise to the opening of the aortic valve, and include such parameters as rate of developed pressure and the maximal velocity of muscle fiber shortening at zero afterload.

Ejection phase indices are measured during the time the aortic valve is open and blood is being ejected from the ventricle (these are not necessarily the same). Commonly used ejection phase indices include ejection fraction (the proportion of blood in the ventricle ejected with each contraction) and the mean velocity of circumferential fiber shortening, the mean rate at which the left ventricular muscle shortens, normalized for left ventricular circumference at the onset of ejection.

Unfortunately, no measure of left ventricular function has been satisfactorily shown to reflect myocardial contractility without being affected by loading. Therefore, the assessment of left ventricular function, in the patient receiving a potential myocardial depressant such as ADM, is subject to some uncertainty. Preload and afterload may vary

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Preload: Resting fiber length, approximated by left ventricular filling pressure or resting left ventricular cavity volume (EDV).

Afterload: Radius ✖ pressure = myocardial wall tension. (The relation between EDV and the radius of the left ventricle by definition prevents independence of preload and afterload.)

Contractility: Strength of action-myosin interactions.

FIGURE 1.—Cardiac performance.

with dehydration, anemia, transfusion, fever, and other sequelae of neoplastic disease or therapy.

In practice, however, serial application of noninvasive techniques for estimation of left ventricular function has produced consistent results. Several techniques (fig 3) offer themselves for use in the oncology patient including physical examination, systolic time intervals and other external pulse recordings, electrocardiogram (ECG), echocardiography, and recently, gated blood pool radionuclide cineangiography.

Physical Examination

Although it tends to be ignored as a subjective and imprecise method of assessment of cardiac function, physical examination of the heart when properly performed by an adequately trained observer provides early indication of left ventricular dysfunction, without the requirement of costly equipment and technician time. In a patient receiving ADM, the new onset of ventricular (S3) and/or atrial (S4) diastolic gallops may suggest abnormal left ventricular pressure-volume relations (decreased "compliance"). In the absence of fever, a dicrotic pulse may indicate low cardiac output.

I. Isovolumic Indices

A. Rate of rise of intraventricular pressure
(1) dP/dt afterload - ↓
tachycardia - ↑
preload - ↑
(2) Peak dP/dt/LVEDV } attempted corrections
dP/dt/P } for preload
(3) PEP - related to dP/dt, noninvasive

B. Force-velocity parameters
Extrapolated velocity of shortening at "zero" load
(1) Vmax - total pressure
(2) Vmax - developed pressure

II. Ejection Phase Indices
A. Ejection fraction: (EDV-ESV)/EDV
B. Mean VcF
C. Fractional shortening
D. Velocity of posterior wall motion

FIGURE 2.—Left ventricular function. dP/dt = rate of rise of intraventricular pressure; LVEDV = left ventricular end-diastolic volume; dP/dt/P = dP/dt per given developed pressure; Vmax = theoretic maximal velocity of fiber shortening at a zero load; EDV = end-diastolic volume; ESV = end-systolic volume; VCF = mean velocity of circumferential fiber shortening.

A. Physical Examination

Atrial and ventricular diastolic gallops, presystolic apical wave, heart rate, estimated jugular venous pressure, rales, dicrotic pulse

B. ECG

Total electrical activity (summated QRS voltage)

C. Exercise Tolerance Testing With VO_2

D. Phonocardiography and External Pulse Recording

Apexcardiography: a/h ratio
"Calibrated" apexcardiography

Systolic Time Intervals

PEP, LVET, PEP/LVET

E. Echocardiography

LV, RV, LA sequential dimensions wall motion analyses; fractional shortening, ejection fraction, VcF, velocity posterior wall motion; compliance estimate

F. Radionuclide Cineangiography

Global ejection fraction at rest and with exercise

FIGURE 3.—Noninvasive assessment of cardiac performance. VO_2 = peak oxygen consumption; a/h ratio = ratio of the amplitude of the presystolic apical "a" wave to the total deflection of the apexcardiogram; LV = left ventricular; RV = right ventricular; LA = left atrial; VcF = mean velocity of circumferential fiber shortening.

Although echocardiography is a sensitive technique for the detection of pericardial effusion, the bedside signs of elevated venous pressure, and more specifically an exaggerated pulsus paradoxus, are of importance in determining if that effusion is producing cardiac compression. However, care must be taken not to misinterpret certain physical signs. Elevated neck veins may indicate superior vena cava obstruction rather than elevated right atrial pressure, and the presence of rales may suggest atelectasis or pneumonitis, as well as sufficiently elevated left ventricular filling pressure to produce intra-alveolar transudation.

Systolic Time Intervals

Since the external recording of the carotid pulse contour closely approximates the intra-aortic pulse contour, timing of systolic events may be performed accurately and noninvasively. Weissler et al (2,3) have been active proponents of the use of systolic time intervals to assess left ventricular function. The ratio of pre-ejection period to left ventricular ejection time (PEP:LVET) has, in some patients, correlated well with ejection fraction, stroke volume, and cardiac output. In that the PEP includes the isovolumic contraction time and is therefore proportional to the rate of rise of left ventricular pressure (dP/dt), the ratio of PEP:LVET reflects cardiac performance during isovolumic systole and

left ventricular ejection. Commonly, the carotid pulse is recorded with a hand held pick-up and recorded simultaneously with the phonocardiogram and ECG. Unlike echocardiography, technically satisfactory tracings can be obtained in almost all patients. Prolongation of the PEP:LVET ratio has been noted in patients receiving ADM (4).

Several papers in this issue will address the topic of systolic time intervals in ADM cardiomyopathy. However, systolic time intervals only indirectly reflect various aspects of left ventricular performance, in contrast to echocardiography and radionuclide cineangiography, which directly image left ventricular wall motion. Systolic time intervals are therefore not unexpectedly sensitive to many factors (5). For example, both increased left ventricular end-diastolic pressure and decreased aortic diastolic pressure tend to shorten PEP. Consequently, in severe left ventricular muscle failure, particularly in the presence of concomitant fever, the expected prolongation of the PEP due to decreased left ventricular pressure rise time of the injured myocardium would, theoretically at least, be counteracted by the effects of high left ventricular filling pressure and a low aortic diastolic pressure related to fever.

Similarly, decreased venous return, sudden elevation of blood pressure, or left ventricular conduction defect may prolong the PEP despite unimpaired contractility. Although elevation of the blood pressure increases both the PEP and LVET, thus tending to maintain the PEP:LVET ratio, decreased venous return may increase the PEP but decrease the LVET, actually increasing the ratio of these parameters. These considerations may make the interpretation of an increased PEP:LVET ratio as an index of impaired left ventricular contractility hazardous.

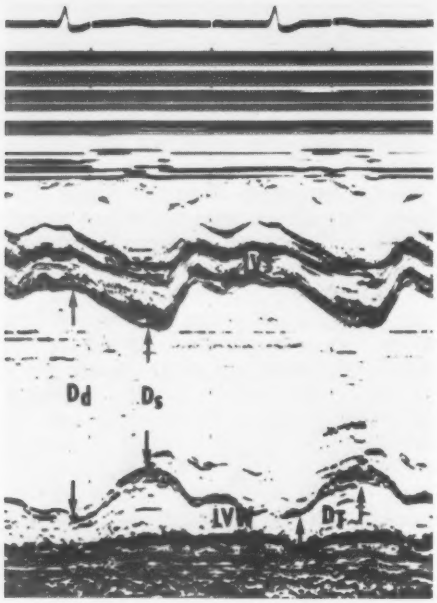
Apexcardiography

The external recording of the cardiac apical impulse is similar to the left ventricular pressure contour, such that measurement of temporal events may be made noninvasively. Of additional interest is the advent of so-called calibrated apexcardiography which measures the changes in precordial pressure relative to an arbitrary calibration pressure (6). While the recorded pressure in no way reflects intraventricular cavitary pressures, the rate of rise of precordial pressure (dP/dt) may correspond to intraventricular dP/dt and show appropriate directional changes in response to inotropic and depressant interventions.

Echocardiography

Examination of the heart with reflected ultrasound has undergone remarkable growth in the past several years. A transducer with an ultrasound frequency of 2.25 mHz, commonly used in examinations in adults, allows tissue penetration of 10 cm with a 1-mm resolution. Sampling of wall motion at 1000/second provides a more continuous record than is possible with contrast angiography, which even with cineangiography offers a filming rate of approximately 60 frames/second. Unlike contrast angiography, only small portions of the left ventricle can be imaged at one time by conventional M-mode echocardiography. Of particular importance in following patients receiving ADM is the care that must be taken to ensure reproducible left ventricular dimensions by conducting the echocardiographic examination in a standard manner (7), and selecting fixed landmarks for measurement (fig 4) of left ventricular dimensions. Since only a small portion of the left ventricle is imaged by the echocardiogram, estimation of left ventricular volumes assumes that the end-diastolic and end-systolic dimensions closely approximate the minor axis of a prolate ellipse of revolution (8). That this may not always be the case, as well as considerable variation in left ventricular geometry, can lead to significant errors in echocardiographic estimation of left ventricular volumes. However, use of fractional shortening (fig 4) instead of ejection fraction, which requires artificial estimation of volumes, circumvents some of these objections. Although cardiac output may be estimated by echocardiograms, a ± 30-ml error in stroke volume at a heart rate of 100/minute can lead, for example, to an unacceptable cardiac output error of ± 3.0 liters/minute. LVET, determined from the simultaneous carotid pulse recording or from inspection of the duration of aortic valve opening or left ventricular wall excursion, can be incorporated into the measurement of the left ventricular dimensions in order to estimate the mean velocity of circumferential fiber shortening. It is unclear, however, whether this measurement importantly enhances the value of fractional shortening alone as an echocardiographic ejection phase index of left ventricular performance.

While not directly related to myocardial function, estimation of serial left atrial dimension and left ventricular wall thicknesses is of value in following patients receiving a drug which may have adverse cardiac effects. A decrease in the early diastolic mitral valve closing slope may suggest left ventricular compliance abnormality (9). Early closure of the aortic leaflet on the echocardiogram may correspond with decreased forward cardiac output.



$$\% \text{ FS} = \frac{Dd - Ds}{Dd} \times 100$$

$$\text{EF} = \frac{Dd^3 - Ds^3}{Dd^3} \times 100$$

$$\text{VcF} = \frac{Dd - Ds}{Dd \times dt} \text{ circ/sec}$$

$$\text{LVM gm} = [(Dd + IVS + LVW)^3 - Dd^3] \times 1.05$$

FIGURE 4.—Echocardiogram showing left ventricular dimensions. FS = fractional shortening; Dd = end-diastolic dimension; Ds = end-systolic dimension; EF = ejection fraction; VcF = mean velocity of circumferential fiber shortening; Dt = duration of anterior motion of posterior left ventricular wall; circ/sec = circumferences/second; LVMgm = left ventricular mass in grams; IVS = interventricular septal thickness; LVW = posterior left ventricular wall thickness. The specific gravity of muscle is 1.05 g/ml.

Unfortunately, the very features which make echocardiography attractive may also lead to an abuse of this diagnostic technique. While the ready availability of echocardiographic equipment and the apparent ease of examination encourage the frequent use of this technique, careful training of personnel performing the examination, as well as those who interpret the echocardiographic record, is mandatory to avoid overinterpretation and misinterpretation of studies. Even with experienced technicians, studies inadequate for quantitative measurement of left ventricular dimensions may be obtained in perhaps 30% of adult patients.

Of further concern, the presence of left ventricular dyssynergy renders the small M-mode echocardiographic sample of left ventricular wall motion inadequate for estimation of systolic left ventricular function. Two-dimensional echocardiography allows imaging of a larger segment of the heart. Unfortunately, the relatively poor resolution of this technique has limited its usefulness for quantitative analysis of left ventricular performance.

Radionuclide Cineangiography

ECG-gated cardiac blood pool scanning allows real-time imaging of the left ventricle. Since the left ventricular blood volume is proportional to the chamber blood radioactivity, changes in left ventricular radioactivity versus time may be plotted which actually reflect volume versus time (10). Although absolute left ventricular volumes cannot at present be computed, as can be done with contrast angiography, the relative volume change between end-systole and end-diastole, ie, ejection fraction, can be determined. Reliable results may be obtained after as little as 1 minute of imaging, allowing the assessment of left ventricular performance during exercise as well as at rest. Although the test is not strictly "noninvasive," requiring peripheral venipuncture for injection of the radiopharmaceutical, it certainly confers less discomfort, risk, and technical difficulty than contrast angiography, which requires catheterization of the left ventricle. Of further benefit, the ejection fraction obtained by cardiac scintigraphy does not require questionable assumptions of left ventricular geometry, as do echocardiography and contrast left ventriculography. Potential effects of contrast material itself on left ventricular function are eliminated from consideration. In some patients, particularly those with ischemic heart disease, a normal resting ejection fraction may decrease with supine bicycle exercise, and regional wall motion abnormalities may appear.

Whether exercise improves the diagnostic usefulness of radionuclide cineangiography in patients receiving ADM is as yet uncertain. Application of this technique to the study of ADM effects on the heart is discussed elsewhere in this issue by Drs. Kennedy, Singer, and associates.

CONCLUSIONS

It is hoped that this brief review will serve to acquaint the noncardiologist with some of the difficulties, both conceptual and technical, in evaluating cardiac function. The search for the ideal technique for evaluation of left ventricular function is elusive, largely because performance of the heart cannot be completely defined in any single way. Noninvasive methods are not "second string" to cardiac catheterization, attractive only for their lack of morbidity, but may provide information of a different nature, which may supplement or in some instances supplant invasive modalities. Because the various noninvasive techniques look at different aspects of cardiac performance, serial use of several of these tests may enhance their diagnostic power.

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Overview of Cardiac Pathology in Relation to Anthracycline Cardiotoxicity

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SUMMARY

A review is presented of cardiac pathologic changes associated with acute and chronic toxicity of anthracyclines. These changes consist of cardiac dilatation, degeneration and atrophy of the muscle cells, and interstitial edema and fibrosis. The degeneration of cardiac muscle cells is a complex phenomenon that involves the myofibrils, the nucleus, the mitochondria and the membrane systems of the T-tubules, the sarcoplasmic reticulum, and the intercellular junctions. The pathogenesis of these alterations is discussed in terms of the biochemical effects of anthracyclines.

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The clinical use of daunorubicin (DNR) and adriamycin (ADM), two antineoplastic agents of the anthracycline type, has been limited by the development of clinical and histopathologic evidence of cardiotoxicity. The cardiotoxic effects can be subdivided into acute and chronic depending upon their temporal relationship to the administration of the drugs. The acute effects are characterized by hypotension, tachycardia, and various arrhythmias which develop within minutes after iv administration (1). In contrast, the chronic effects develop only after several weeks or months of treatment, sometimes having their onset after the course of therapy has been completed. These chronic, delayed effects are manifested by the insidious onset of severe, often fatal congestive heart failure.

In reviewing the cardiac morphologic changes produced by anthracyclines, it is important to try to relate such changes to the biochemical effects that these agents are known to induce in the myocardium. This is difficult because of the multiplicity and complexity of the biochemical changes involved. Among these are: (*a*) binding of anthracyclines to nuclear and mitochondrial DNA, with subsequent inhibition of RNA and protein synthesis (2); (*b*) inhibition of Na-K-dependent ATPase activity (3); (*c*) inhibition of reactions utilizing coenzyme Q (4); (*d*) alterations in calcium transport and in intracellular electrolyte balance (5); (*e*) chelation of divalent cations (5); and (*f*) promotion of lipid peroxidation by means of reactions mediated by free radicals (6). The time course of these various effects has not been completely elucidated. Nevertheless, it seems reasonable to believe that some of these effects are more important in acute toxicity and others in chronic toxicity.

Acute Cardiotoxicity of Anthracyclines

Some of the acute effects of anthracyclines, ie, the peripheral vascular effects, are consequences of drug-induced release of histamine and catecholamines. Morphologic changes related to the arrhythmias remain to be determined, although it is known that in chronic toxicity of ADM the specialized conducting cells of the rabbit heart show lesions similar to those in ordinary working myocardium (7). The only cardiac morphologic change that has been found to occur very shortly after administration of ADM is the development of nucleolar segregation (8,9). This change has been observed in mouse myocardium (8) as early as 10 minutes after a single injection of 10 mg of ADM/kg of body weight. Similar changes occur in mouse and rat hepatocytes and in rat ventricular myocardium after the administration of single large doses of ADM (8,9). These nuclear changes are in accord with observations showing that (*a*) ADM and DNR penetrate rapidly into cells and bind to nuclei where they can be detected (10,11) by fluorescence microscopy (both drugs impart a reddish fluorescence to

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nuclei), and that (*b*) the nuclear binding involves intercalation of the drugs into nuclear DNA and results in inhibition of nucleic acid and protein synthesis (2). Thus, these observations show that anthracyclines produce acute toxic effects on nuclei. The long-term significance of nucleolar segregation is unclear because the morphology of nucleoli returns to normal by 14 hours after administration of ADM (8). Nuclear lesions have been observed only in a small percentage of cardiac muscle cells in patients dying of chronic anthracycline toxicity (10,12). These lesions consist of various degrees of unraveling of nuclear chromatin fibers into fine fibrils and filaments. These changes occur in conditions other than anthracycline toxicity (12). Such changes have not been described in experimental animals given anthracyclines in vivo, although they were reproduced in vitro in monkey myocardium (10). Highly detailed histochemical and ultrastructural studies of cardiac muscle cell nuclei have not been reported in animal models of anthracycline toxicity. These observations suggest that cumulative damage to DNA in cardiac muscle cells (which are not capable of reproducing themselves, thereby diluting the damage to the genetic material) can result from the administration of repeated doses of anthracyclines, and that such damage (possibly including single-stranded and double-stranded breaks in DNA) may not be repaired properly by cardiac muscle cells, thus leading to severe interference with protein synthetic processes. Since the half-life of contractile proteins in cardiac muscle is in the range of 1–2 weeks, these effects may be of crucial importance in the pathogenesis of anthracycline-induced cardiomyopathy.

Chronic Cardiotoxicity of Anthracyclines

The morphologic changes observed in chronic cardiac toxicity of ADM and DNR consist of (*a*) cardiac dilatation and, less frequently, mural thrombosis; (*b*) degeneration and atrophy of cardiac muscle cells; and (*c*) interstitial edema and fibrosis. The cardiac dilatation and mural thrombosis are similar to those seen in patients with the idiopathic type of congestive or ventricular-dilated cardiomyopathy. The degeneration of cardiac muscle cells can assume two forms; the first type is characterized by myofibrillar loss so that, by light microscopy, the affected cells appear pale-staining (but nonvacuolated), and the second type is manifested by marked cytoplasmic vacuolization, usually associated with myofibrillar loss. The reasons for these variations in the response of different cells to the same stimulus remain unknown.

The features just described are similar in man (10,12–14) and in the rat (15), mouse (8,16), and rabbit (5,17) models of ADM cardiotoxicity. These changes appear to be related to the total cumulative dose and to the time scheduling of the individual doses. Such changes can begin to develop, at least in mouse myocardium, within 24 hours after the administration of a large, single dose of ADM (8). When smaller, repeated doses are given, the changes take several weeks or months to develop. Three facts need to be emphasized with respect to the dose-cardiotoxicity relationships. First, the main target organs in very acute toxicity are the gastrointestinal tract and the bone marrow, and lesions in these organ systems can cause death before the characteristic morphologic changes of cardiotoxicity have had a chance to develop. Second, there is significant variation in the severity of morphologic changes demonstrated by different patients or experimental animals in response to a given dose level. Third, the early lesions are focal, becoming more diffuse as their severity increases. In histologic preparations, the cytoplasmic vacuolization is detected more easily than is the myofibrillar loss. This is especially true of sections stained with hematoxylin and eosin. Mild degrees of cytoplasmic vacuolization can also be overlooked in histologic sections. Light microscopic examination of tissues fixed with glutaraldehyde, embedded in plastic resins, sectioned at a thickness of 1 μ, and stained with alkaline toluidine blue offer considerably greater histologic detail than do routine histologic sections.

Electron microscopic studies (8–10,12–17) have shown that the degeneration of cardiac muscle cells in chronic anthracycline toxicity is a complex phenomenon that involves the myofibrils, the nuclei, the membrane systems of the T-tubules, the sarcoplasmic reticulum and intercellular junctions, and the mitochondria. These alterations are illustrated in figures 1–5. The myofibrils show disruption, with lysis of the myofilaments (figs 1–3). These changes account for the pale staining of the cytoplasm and, at least in part, for the cellular atrophy. The vacuolization of the cytoplasm is mainly due to pronounced swelling of the tubules and cisterns of the sarcoplasmic reticulum (fig 1); accumulation of lipids and dilatation of the transverse tubular system also contribute to the vacuolated appearance. The intercellular junctions undergo dissociation, with formation of hemidesmosomes (fig 4), intracytoplasmic junctions, and spherical microparticles. The hemidesmosomes are derived from the separation of desmosomes. The intracytoplasmic junctions are formed by the specialized apposition of two parts of the plasma membrane of the same cell, and

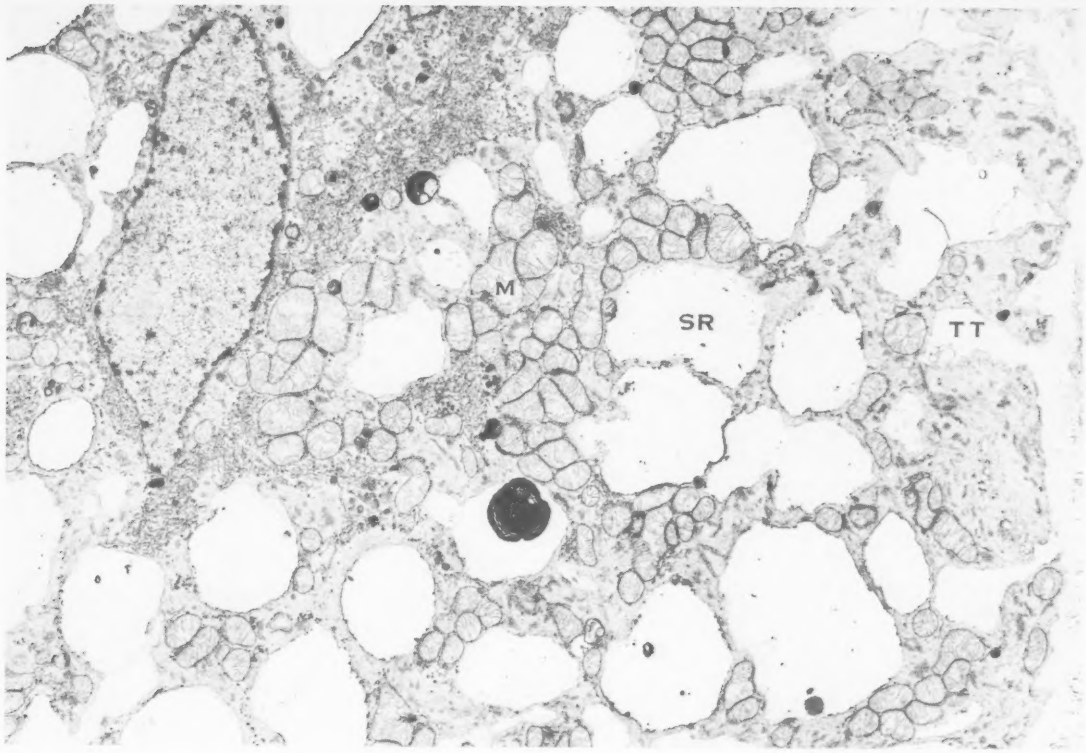

FIGURE 1.—Electron micrograph of highly vacuolated cardiac muscle cell from a rabbit given a total dose of 400 mg of ADM/m². The vacuolization is due mainly to swelling of sarcoplasmic reticulum (SR) and, to a lesser extent, to dilatation of the transverse tubular system (TT). Extensive loss of myofibrils has taken place, and most of the cytoplasm is occupied by mitochondria (M). Filamentous material is seen in the nucleus (upper left). Some remnants of myofibrils are shown at upper right (× 7000).

probably result from the rearrangement of remnants of specialized components of previously present intercellular junctions (18). Spherical microparticles (fig 5) are related to the remodeling of plasma membranes, especially in areas of cellular dissociation (19). The mitochondria have been found to show a variety of changes, including pleomorphism, decrease in overall size, alterations in the density of the matrix, and formation of concentric lamellae (myelin figures) composed of electron-dense material. Mitochondrial inclusions have been observed in human myocardium obtained at necropsy (10,13). Such inclusions, which are of the amorphous or flocculent type and not of the calcium-containing type, are related to postmortem autolysis (10). Calcium-containing intramitochondrial inclusions have not been demonstrated unequivocally in ADM- or DNR-treated animals. Some of the myelin figures are associated with dense bodies which probably are derived from lysosomes. Mitochondrial changes appear more prominent in acute than in chronic toxicity, while the reverse is true of alterations in sarcoplasmic reticulum, which are minimal in the acute lesions. The interstitial edema is in accord with observations showing that cardiac tissues in ADM toxicity have an increased content of water, sodium, and calcium (5). The interstitial fibrosis is difficult to evaluate because the cellular atrophy exaggerates the prominence of the interstitial connective tissue. Inflammatory reaction is usually absent or minimal and limited to the presence of small numbers of macrophages. Endothelial damage has been observed in rats and mice but not in rabbits.

Pathogenesis of Cardiac Morphologic Changes Induced by Anthracyclines

The pathogenesis of the changes enumerated above has not been fully elucidated, but it seems

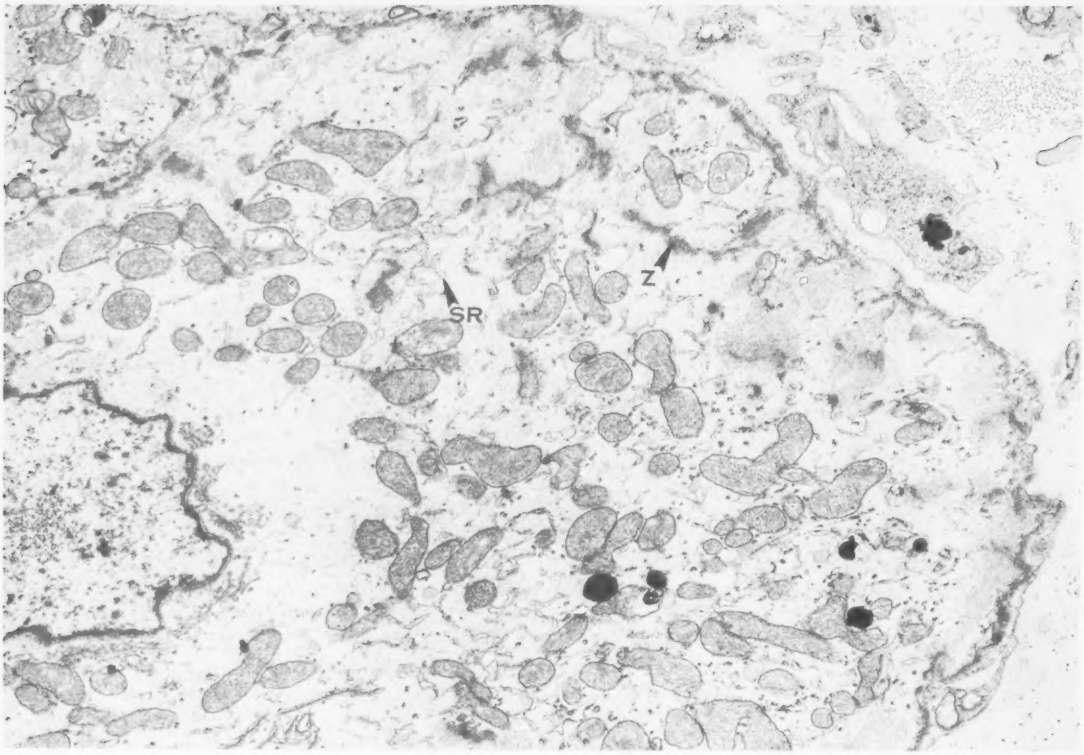

FIGURE 2.—Parts of 2 cardiac muscle cells from same rabbit described in fig 1, showing severe loss of myofibrils but without associated dilatation of sarcoplasmic reticulum or T-tubules. The sarcoplasmic reticulum (SR) forms a fine network of tubules in areas free of myofibrils. Remnants of Z-bands (Z) are present in several areas together with partially lysed myofilaments. Mitochondria appear smaller than usual in size. Small particles present throughout cytoplasm are ribosomes (× 10,800).

likely that several different drug effects are important. As mentioned previously, the myofibrillar loss probably results from interference with protein synthesis and the nuclear changes probably result from the binding of ADM or DNR to nuclear DNA. The pathogenesis of changes involving the membrane systems of the cell is less clear. Such changes also may be related to the inhibition of protein synthesis, with subsequent interference with normal turnover of proteins in membranes, but other evidence suggests that peroxidation of membrane lipids may be an important factor. ADM and DNR can initiate lipid peroxidation by facilitating the transfer of electrons from endogenous compounds such as NADPH to oxygen, resulting in the formation of superoxides that can decompose to hydroxy radicals, peroxy radicals, and hydrogen peroxide; these in turn can oxidize unsaturated fatty acids in membranes to lipid peroxides (20). Two observations by Myers and collaborators (6,20) indicate that lipid peroxidation may play a role in the pathogenesis of anthracycline toxicity. The first observation is that the administration of very large doses of α-tocopherol (vitamin E, a free radical scavenger) reduces significantly the acute toxicity and mortality of ADM in the mouse (20), and the second is that malondialdehyde, a product of the peroxidation and subsequent decomposition of unsaturated fatty acids, is readily detected in the hearts of mice for 2–6 days after the administration of ADM, but not in the hearts of control animals or of animals treated with both ADM and α-tocopherol (6).

Ubiquinone, which acts as a free radical scavenger and also as an antagonist to the inhibitory effect of anthracyclines on reactions mediated by coenzyme Q, also has been reported to ameliorate considerably acute cardiotoxicity and to decrease chronic toxicity of ADM (21). It is of special interest to note that exposure of guinea pigs, rabbits, and hamsters to 100% oxygen, at atmospheric pressure

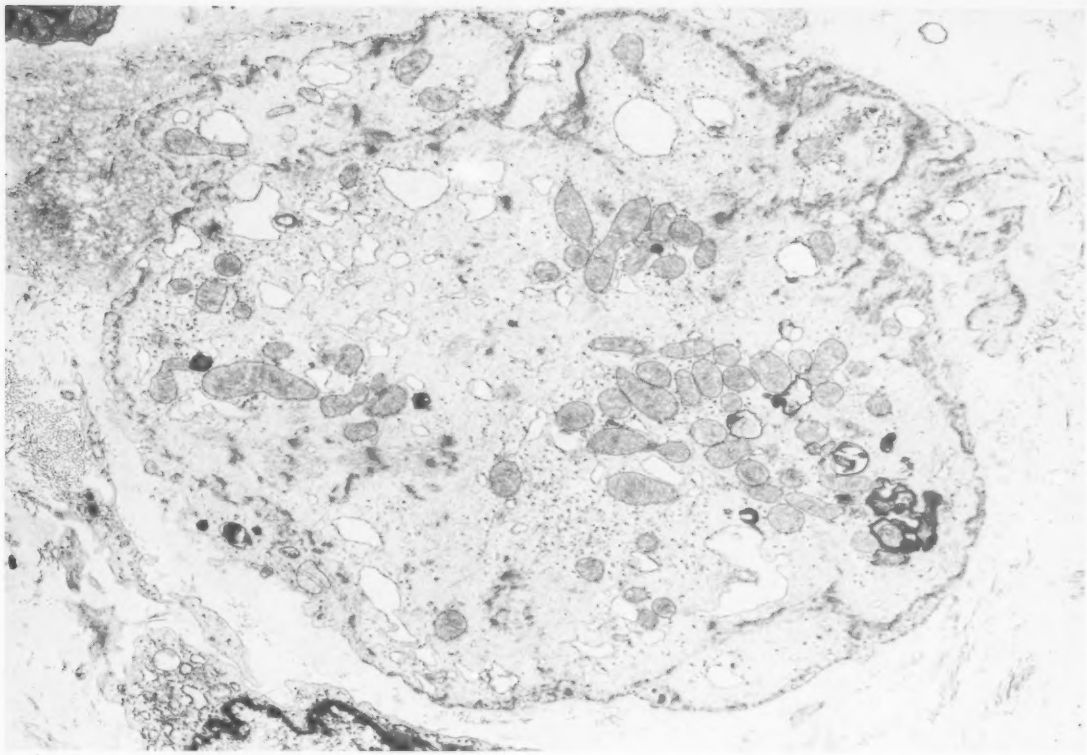

FIGURE 3.—Another cardiac muscle cell from the same rabbit described in figs 1 and 2 shows loss of myofibrils associated with moderate dilatation of sarcoplasmic reticulum. Note myelin figures at lower right. This cell shows a combination of the features illustrated in figs 1 and 2 (× 7000).

and room temperature for < 1 week, induces skeletal muscle and cardiac muscle lesions characterized by dilatation of sarcoplasmic reticulum, focal myofibrillar lysis, mitochondrial damage, accumulation of lipid droplets, and formation of myelin figures (22). Vascular lesions are not associated with these changes. Although their exact pathogenesis is not clear, these lesions resemble in several respects those produced by anthracyclines, and it is possible that they are mediated by peroxidation damage to membrane systems. Edema in anthracycline toxicity may be the result of increased permeability of damaged membranes, with subsequent calcium overload and increases in the tissue content of sodium and water. The inhibition of Na-K ATPase may be important in this respect. Dilatation of sarcoplasmic reticulum is a nonspecific change that occurs in a variety of conditions in which cardiac muscle cell edema is present. It should be pointed out, however, that the most vacuolated muscle cells in chronic ADM toxicity do not show diffuse cytoplasmic edema, ie, in the main cytoplasmic compartment; in such cells the fluid accumulation appears to be essentially confined to vesicles of sarcoplasmic reticulum. The reasons for this pattern of distribution of intracellular edema are not known.

In contrast to the similarities to the changes produced by oxygen toxicity, the cardiac morphologic changes caused by ADM and DNR are different from those occurring in radiation injury and in deficiency of selenium and vitamin E (Se-E), two conditions in which free radical damage and peroxidation phenomena are thought to play a role in the pathogenesis of the cardiac damage. In radiation injury to the heart, the initial damage is most prominent in capillary endothelial cells, which become edematous or necrotic; platelet and fibrin thrombi are frequent. In later stages, there is severe interstitial fibrosis, but at no time do the cardiac myocytes show alterations similar to those in ADM toxicity (23). The combined administration of ADM and radiation to rabbits results in the

FIGURE 4.—Hemidesmosome (arrows) is present at surface of cardiac muscle cell (rabbit treated as described in legend to fig 1) in area of cellular dissociation (× 97,000).

FIGURE 5.—Clusters of spherical microparticles occupy space between partially dissociated components of intercellular junction in myocardium of same animal described in fig 4 (× 39,750).

superimposition of lesions typical of each of the two agents and in enhancement of the cardiotoxicity of ADM (24).

Comparison of the pathologic changes produced by ADM and by Se-E deficiency is of interest because Se-E, in conjunction with glutathione peroxidase, form an antioxidant system which prevents the peroxidation of membrane lipids. Cardiac lesions in Se-E deficiency (25,26) have been best characterized in the pig and consist of (*a*) multiple foci of necrosis with hyalinization or with hypercontraction bands and mitochondrial swelling, disruption, and calcification; (*b*) intramyocardial hemorrhage ("mulberry heart"); (*c*) fibrinoid necrosis of small intramural coronary arteries; and (*d*) capillary microthrombi composed of fibrin and platelets. Microthrombi are more frequent in the spontaneously occurring than in the experimentally induced Se-E deficiency state. This pathologic picture differs clearly from that seen in ADM toxicity, which in pigs produces cardiac histologic changes similar to those described in other species (Herman EH, Van Vleet JF, and Ferrans VJ, unpublished observations). The administration of Se-E provides only a modest degree of protection against the chronic cardiotoxicity of ADM in the rabbit (Van Vleet JF, Greenwood LA, and Ferrans VJ, unpublished observations). These data, and the work of Myers et al (20) on the protective effect of vitamin E against the acute toxicity of ADM can be interpreted as indicating that lipid peroxidation is of greater importance in acute than in chronic toxicity, and that the reverse may be true of the changes induced in DNA. It also seems reasonable to conclude from the preceding comparisons that the morphologic features of the toxicity produced by peroxidation and free radical phenomena will vary depending upon the nature and the site of release of the offending compounds.

Relationship Between Clinical and Myocardial Biopsy Findings in Patients With Anthracycline Toxicity

The studies presented by Billingham and co-workers in this issue have provided considerable insight into the problem of anthracycline-induced cardiomyopathy in man. In view of the complex nature of this problem, it is not surprising to find that the correlation between biopsy findings and clinical evidence of congestive heart failure is less than ideal in some patients. In evaluating these discrepancies, the following factors can be identified as presenting limitations to the usefulness of myocardial biopsy in predicting which patients will develop cardiomyopathy as a consequence of anthracycline therapy:

1. The method of biopsy rating used by Billingham et al places considerable emphasis on recognition of vacuolization of muscle cells, but gives relatively little importance to myofibrillar loss and other cellular alterations, and omits fibrosis from consideration.
2. Variations due to tissue sampling can occur because of the focal nature of the lesions, particularly those occurring at lower dose levels.
3. It remains to be determined, in man as well as in experimental animals, how representative of the state of the whole heart are tissue samples taken from the subendocardial area of the right side of the ventricular septum.
4. Variations also occur in the biologic responses (manifested either as tissue damage, congestive heart failure, or a combination of both) of different patients to a given cumulative dose of anthracyclines.
5. Factors other than anthracycline toxicity (cachexia, anemia, hypoproteinemia, infection) can contribute to the development of congestive heart failure in patients with neoplastic disease.

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Adriamycin-Induced Cardiac Dysrhythmias in an Experimental Dog Model[1]

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SUMMARY

Adriamycin (ADM) is a widely used antineoplastic agent. Serious toxicity in the form of a dose-dependent cardiomyopathy is well known. Reports of an increased incidence of sudden death in conjunction with ADM therapy suggest that it may also cause serious cardiac dysrhythmias. There is, however, very little concrete information in this regard. Systematic studies, using repetitive Holter monitoring and in vivo electrophysiologic techniques, were carried out on ten dogs to assess the effects of short-term "high-dose" and long-term "low-dose" ADM administration on cardiac electrical activity, particularly with respect to rhythmogenesis. Possible relationships between the appearance of dysrhythmia and the development of cardiomyopathy, as defined histologically, as well as selected hemodynamic effects were also examined. ADM administration resulted in the appearance of ectopic rhythms and/or A-V block in 80% (eight of ten) of the entire group of dogs. In four dogs exposed to short-term high-dose ADM infusion (80 mg/m²/day × 3 days), 50% developed high-grade ventricular dysrhythmias, including paroxysmal rapid ventricular tachycardias. All six dogs in the long-term low-dose group (25 mg/m²/week for periods up to 20 weeks) developed ventricular dysrhythmia, with high-grade activity (slow and rapid ventricular tachycardia) occurring in 80% (five of six dogs). Atrial fibrillation and second-degree A-V block also occurred, but much less commonly (20% and 40% of the total group respectively). Hemodynamic and electrocardiographic monitoring during drug infusion revealed development of sustained sinus tachycardia (28% increase in sinus rate compared with control values for both low- and high-dose groups) and a transient period of systemic arterial hypotension (42% and 21% reduction in mean arterial pressure for high- and low-dose dogs respectively). Ectopic activity was not noted to occur during the actual infusion. Pathologic studies on specimens of atrium, specialized ventricular conducting tissues, and ventricular myocardium revealed a spectrum of cardiomyopathic changes ranging from normal myocardium to those indicative of severe injury. There was wide individual variability in observed changes for equivalent doses. Relationships between dysrhythmia, particularly ventricular dysrhythmia, and histologic changes were equivocal. Insofar as the findings in the dog are applicable to man, they provide suggestive evidence in support of conclusions that ADM exerts significant rhythmogenic effects and that serious

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cardiac dysrhythmias, particularly ventricular dysrhythmias, may represent an important complication of drug therapy. Occurrence of ventricular dysrhythmias would provide a possible explanation for a reported increase in the incidence of sudden death in ADM-treated patients. Transient hypotension during drug infusion could also contribute to sudden death. Since it appears that ventricular dysrhythmia may antedate pathologic changes, the former may serve to herald the onset of cardiomyopathy. Systematic clinical studies designed to assess the rhythmogenic effects of ADM therapy in man are indicated.

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The anthracycline antibiotic adriamycin (ADM) is an effective and widely used antineoplastic agent. To date, the major factor limiting its clinical usefulness has been its association with adverse cardiac effects (1). Toxic effects have generally been manifested in three ways: (*a*) a severe and often fatal congestive cardiomyopathy when cumulative dose levels of > 550 mg/m^2 of body surface area are reached (2); (*b*) non-dose-related electrocardiographic (ECG) contour abnormalities including axis shifts and nonspecific repolarization changes (3); and (*c*) atrial and ventricular dysrhythmias (4). ECG changes have been observed in 9%–26% of the patients undergoing ADM therapy (4,5). In a study of 472 adults treated with ADM, O'Bryan et al (5) found changes in 43 patients (9%), four of whom were reported to have sustained "sudden death" early in the course of therapy, possibly due to ventricular dysrhythmia.

Despite the rhythmogenic potential of ADM, most large reviews, including those dealing with its cardiotoxic properties, have not specifically addressed the issue of sudden death (4,6), nor has there been any systematic study of the incidence of potentially lethal cardiac dysrhythmias. The fact that ADM is generally used in combination with other potentially cardiotoxic chemotherapeutic agents renders clinical assessment of its specific effects difficult. We have therefore chosen to systematically study the rhythmogenic activity of ADM by means of repetitive Holter monitoring (7) and in vivo electrophysiologic techniques in a dog model. The effects of long- and short-term drug administration and dose relationships are defined. Possible electrophysiologic-pathologic correlations are considered.

METHODS AND MATERIALS

In Vivo Studies

Eight mongrel pound dogs and two beagles (weighing between 10 and 22 kg) that were judged to be free of ectopic atrial and ventricular ectopic activity or A-V block on the basis of a 16-hour Holter monitoring recording obtained under control conditions were studied. The dogs were divided into short-term high-dose and long-term low-dose groups. The high-dose group consisted of four dogs, each given ADM at a dose of 80 mg/m^2 by slow iv infusion over 10 minutes for 3 consecutive days. Prior to drug infusion, the animals were anesthetized with iv sodium pentobarbital (30 mg/kg) and ventilated through a cuffed endotracheal tube using a standard Harvard ventilator. Femoral blood pressure was continuously monitored by direct femoral artery cannulation using a Statham P23B gauge. Blood pressure was recorded for 30 minutes prior to and for 3 hours after drug infusion. A single lead ECG was recorded continuously on magnetic tape using a standard-type Holter monitor until the animal was killed at 72 hours.

The low-dose group consisted of six dogs, each given a dose of approximately 25 mg/m^2 of ADM/week by iv infusion until persistent ventricular dysrhythmia developed. Dogs were awake during drug administration except during arterial pressure determinations. In one animal (dog 5), femoral pressure was monitored as above during administration of the first two doses. The ECG was continuously recorded for 16 hours prior to the start of drug therapy (control conditions), and for 16-hour periods twice weekly during the course of drug administration. Drug dosage schedules were sometimes varied in response to change in animal status, particularly evidence of myelosuppression. Meticulous care was exercised to maintain nutrition and electrolyte balance and to protect against infection.

After completion of the prescribed dosage schedule, one high- and three low-dose dogs were anesthetized as described above and in vivo electrophysiologic studies were performed using two standard No. 6F tripolar pacing catheters. One catheter was positioned across the tricuspid valve for recording of the His bundle electrogram (8). The second catheter was placed in the high right atrium for pacing purposes and recording atrial electrograms. Stand-

ard limb lead ECGs and intracardiac electrograms were continuously displayed and recorded on an Electronics for Medicine DR-12 oscilloscopic recorder, using filter settings of 40 and 2000 Hz. Records were recorded on photographic paper at paper speeds of 100 mm/second.

Electrophysiologic parameters were assessed as follows: (*a*) Atrioventricular conduction was defined by means of measurements of A-H and H-V intervals on the His bundle electrogram both during spontaneous beating and at selected paced rates during atrial and ventricular pacing. Note was made of the cycle length at which 1:1 conduction first failed. (*b*) Atrial, A-V junctional, and ventricular refractory periods were determined, both during spontaneous sinus rhythm and at paced rates of 120/minute using standard extra-stimulus techniques. The response to abrupt changes in pacing rate was also assessed in this regard (9). (*c*) Sinus node function was evaluated by measuring the sinus node recovery time after 3 minutes of continuous high right atrial pacing at a rate of 130/minute (10). Estimates of sino-atrial conduction time were also made (10). (*d*) Predisposition to the development of re-entrant type supraventricular and ventricular tachyarrhythmias was defined by using rapid atrial and ventricular pacing and atrial and ventricular extra-stimulus techniques (11,12). Comparisons in each instance were made between values obtained from the studies on drug-treated dogs with those from dogs studied under control conditions.

Histopathologic Studies

After completion of the course of ADM, the low-dose dogs were killed and the hearts excised. Specimens from selected sites were obtained for light and electron microscopic study as follows:

Light microscopic studies.—The dog hearts were fixed in 10% buffered formalin. Random sections were taken from both atria, the left and right ventricular free walls, and the intraventricular septum for light microscopy. Random sections from the specialized A-V conduction system (A-V node, common bundle, and right bundle branch) were also obtained. Tissues were processed in the conventional manner for light microscopic study and stained with hematoxylin and eosin and Masson's trichrome stains.

Electron microscopic studies.—Specimens of ventricular wall for electron microscopic study were obtained directly following cardiac excision, minced finely, and fixed immediately in 2.5% gluteraldehyde and 2% paraformaldehyde in 0.1 M sodium cacodylate buffer (pH 7.2). After fixation, tissues for ultrastructural examination were washed with several changes of cold buffer, post-fixed with cold 2% osmium tetroxide, stained en bloc with 2% uranyl acetate, and embedded in epoxy resin. Semithin sections of Epon-embedded tissue were cut using an LKB III ultratome, stained with toluidine blue, and examined by light microscopy for purposes of block selection. Ultrathin sections were then stained with lead citrate and examined with a Hitachi H4 IIA electron microscope at 50 KV. Ten blocks were examined for each dog.

ECG Analysis

Magnetic ECG tapes were analyzed at 60 × real time using an Avionics "Electrocardioscanner." One-minute rhythm strips were obtained at hourly intervals. In addition, a minute rhythm strip was obtained during the period of peak dysrhythmia in each hour. The rhythm strips were carefully analyzed in real time. Average sinus rates were defined and determinations were made of average P-R, QRS, and Q-T intervals, at a constant cycle length of 600 msec, in each rhythm strip. All instances of supraventricular and ventricular ectopic activity and A-V and intraventricular conduction disturbances were documented. At times when bursts of ectopic supraventricular and ventricular tachycardia (defined as three or more ectopic beats in succession) occurred, duration and rate of such runs were noted. Semi-quantitative estimates of the frequency of ectopic activity were made by determining the average number of ectopic beats per hour during each monitoring period.

RESULTS

Studies on ten dogs showed that (*a*) ADM administration resulted in an acute increase in sinus rate, a transient fall in blood pressure, and delayed development of persistent ectopic atrial and ventricular dysrhythmias together with variable depression of A-V conduction; (*b*) the severity of the rhythm changes did not appear to be directly dose-dependent; and (*c*) there was no consistent relationship between the character and severity of dysrhythmia and cardiomyopathic pathologic changes. Findings in both high-dose and low-dose dogs were comparable. There were no clear-cut differences demonstrable between beagles and mongrel pound dogs.

Cardiac Rate and Rhythm Changes

Sinus rate.—ADM infusion was associated with a prompt and sustained increase in sinus rate. This

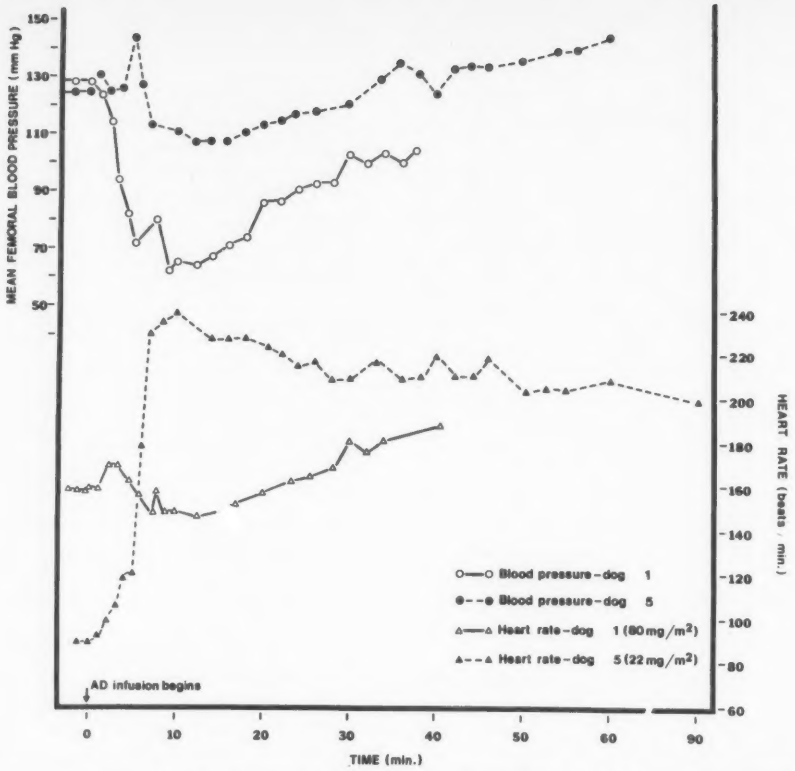
MEAN FEMORAL BLOOD PRESSURE (mm Hg)
HEART RATE (beats · min.)
TIME (min.)
Blood pressure-dog 1
Blood pressure-dog 5
Heart rate-dog 1 (80 mg/m²)
Heart rate-dog 5 (22 mg/m²)
ADM infusion begins

FIGURE 1.—Blood pressure (○ and ●) and heart rate (△ and ▲) responses to ADM infusion in representative high-dose (dog 1) and low-dose (dog 5) dogs. The time, in mins, is depicted on the abscissa. Mean arterial pressure, in mm Hg, and heart rate, in beats/min, are shown on the left and right hand ordinates respectively. Infusion was started at time indicated by (↓) and lasted 10 mins. Note the acute fall in mean arterial pressure and sustained increase in heart rate which characterized both groups. *See* text for details.

was true for both the high- and low-dose dogs and for the anesthetized and conscious animals. Rate acceleration generally developed within 5 minutes of the start of drug infusion and persisted for up to 4 hours following its cessation (fig 1). In the low-dose dogs, it was possible to compare the sinus rates on days in which the drug was infused with the rates on days in which no drug was given. Sinus rates were found to average 28% higher during the first 3 hours after ADM infusion on drug versus nondrug days (fig 2).

Ectopic dysrhythmia.—None of the dogs in either group exhibited ectopic activity during pretreatment control monitorings. In contrast, eight of ten of the total group of dogs (two of four high-dose and all six low-dose dogs) developed persistent ectopic dysrhythmias during treatment with ADM. Development of dysrhythmia was not temporally related to actual drug infusion in either group. In the low-dose group, dysrhythmia generally was not noted until at least 2 weeks after the start of treatment. The distribution and character of the observed dysrhythmias are defined in table 1 and figure 3.

Ectopic ventricular dysrhythmia.—Two of the four high-dose and all six of the low-dose dogs developed ventricular ectopy (table 1 and fig 3). Ventricular ectopic activity was of two general types: (*a*) fixed coupled ventricular premature contractions (VPCs) and paroxysmal rapid ventricular tachyarrhythmias, and (*b*) accelerated ventricular escape beats and runs of slow ventricular tachycardia. Ventricular ectopy, once it had made its appearance, persisted until the animal was killed. In general, ventricular ectopic beats tended to increase in frequency and to become multiform with increasing duration of treatment. In one of the four high-dose and five of the six low-dose dogs, runs of ventricular tachycardia developed. Isolated VPCs developed in two of the four high-dose and in all of the six low-dose dogs. In one member of the high-dose (dog 3)

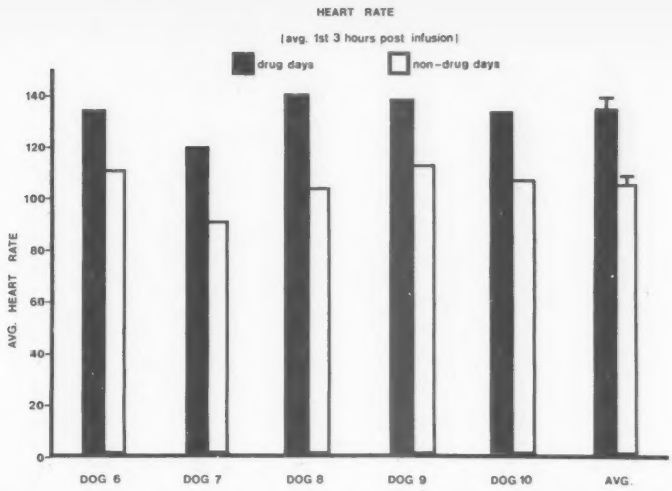

FIGURE 2.—Comparison between average sinus rates, in beats/min, during the initial 3 hrs after ADM administration (filled bars) and during the initial 3 hrs of monitoring on nondrug days (open bars) for 5 representative low-dose dogs. Average rates for the group as a whole are shown on the right (bars designated AVG). Note increased average heart rate on drug compared with nondrug days. *See* text for details.

TABLE 1.—Listing of different types of dysrhythmia observed in combined group of high-dose (4 dogs) and low-dose (6 dogs) ADM-treated animals*

Dog No.†	Atrial dysrhythmia‡		Ventricular dysrhythmia§				A-V block	Onset of dysrhythmia¶	ADM** (mg/m²)
	APC	A.fib	AVE	Slow VT	PVC	Rapid VT			
1	–	–	–	–	–	–	–	—	—
2	–	–	–	–	–	–	–	—	—
3	–	–	+	–	+	+	+	2 days	160
4	+	–	–	–	+	–	+	2 days	160
5	–	–	+	+	+	+	–	2 wks	44
6	–	–	–	–	+	+	+	20 wks	270
7	+	+	+	+	+	–	–	11 wks	210
8	+	+	–	–	+	+	+	19 wks	271
9	–	–	+	+	+	–	–	5 wks	90
10	+	–	–	–	+	–	–	19 wks	247

*The time interval between the initiation of ADM and the onset of persistent dysrhythmia and the cumulative dose at which persistent dysrhythmia first occurred are also shown for each animal. Note that all of the low-dose dogs and 50% of the high-dose dogs developed ≥ 1 type of ventricular dysrhythmia alone or in combination with atrial ectopy and/or A-V block. Development of multiple types of rhythm disturbances was the rule rather than the exception, occurring in 8 of the 8 dogs which developed dysrhythmia. Also note lack of consistent correlation between the occurrence of dysrhythmia and either the cumulative drug doses or duration of drug administration. Beagles (Nos. 7 and 8) did not differ significantly from mixed breed dogs (Nos. 1–6,9,10) with respect to development of dysrhythmia. *See* text for details.

†Dogs 1–4 (high-dose), 80 mg/m² on 3 successive days; dogs 5–10 (low-dose), 20–40 mg/m²/wk.

‡APC = atrial premature contraction; A.fib = atrial fibrillation.

§AVE = accelerated ventricular escape beats; slow VT = slow ventricular tachycardia; PVC = isolated ventricular contractions; rapid VT = rapid ventricular tachycardia.

¶Time to onset of persistent ventricular dysrhythmia.

**Cumulative dose at onset of persistent ventricular dysrhythmia.

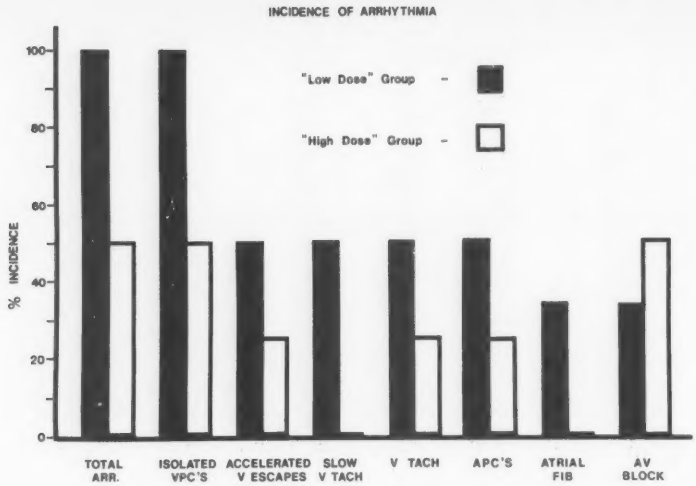

FIGURE 3.—% incidence of dysrhythmia in low-dose (filled bars) and high-dose (open bars) groups of dogs. The incidence of all dysrhythmias, irrespective of type, encountered in both groups of dogs is depicted by the first pair of bars on the left; the incidence of the individual types of rhythm disturbances is shown by the remaining pairs of bars. Dysrhythmias were not noted prior to institution of ADM. Selected rhythm abbreviations: VPC = ventricular premature contractions; V escapes = ventricular escape beats; slow V tach = slow ventricular tachycardia; V tach = rapid ventricular tachycardia; APC = atrial premature contractions; atrial fib = atrial fibrillation; A-V block = second degree A-V block, Mobitz type II. *See* text for details.

and in two members of the low-dose (dogs 5 and 6) groups, VPCs progressed to development of paroxysmal rapid ventricular tachycardias at rates ranging between 180 and 300 beats/minute (fig 4). The onset of paroxysmal rapid ventricular tachyarrhythmias was heralded by the appearance of paired and multiform VPCs. Paroxysmal rapid ventricular tachycardias tended to persist for periods ranging up to 48 hours after which they would subside, to be supplanted by multiform isolated and paired VPCs and accelerated ventricular escape rhythms. In the low-dose dogs, there was no clear-cut relationship between time of onset of VPCs and paroxysmal rapid ventricular tachyarrhythmias and either duration of drug treatment (15–100 days) or cumulative drug dose (44–271 mg/m²) (fig 4A). Accelerated ventricular escape rhythms developed in one high- and three low-dose dogs. The dysrhythmia was characterized by the progressive increase in frequency of such beats, appearance of multiform QRS patterns, and gradual shortening of the escape interval, followed by development of unifocal or multiform slow ventricular tachycardias at rates of 60–75 beats/minute (fig 5). In dogs 5 and 9, two and possibly three types of slow ventricular tachycardia were noted. Once established, slow ventricular tachycardias tended to persist, the frequency and intrinsic rate increasing with increasing duration of treatment. As was the case for VPCs and paroxysmal rapid ventricular tachyarrhythmias, there was no consistent relationship between the time of onset of the dysrhythmia and either the duration of therapy (14–77 days) or the cumulative drug dose (44–271 mg/m²).

Ectopic atrial dysrhythmia.—Ectopic atrial dysrhythmias also developed but were much less frequent (table 1), isolated atrial premature contractions (APCs) (peak incidence, 4/minute) being noted in only one high-dose (No. 4) and three low-dose (Nos. 7, 8, and 10) dogs, and paroxysmal rapid atrial fibrillation being noted in only two low-dose dogs (Nos. 7 and 8) (fig 6). In contrast to ventricular dysrhythmia, atrial ectopy generally, but not always, occurred at higher cumulative doses, ie, high-dose dog No. 4 (160 mg/m²) and low-dose dogs 7 and 8 (287 and 271 mg/m² respectively). However, in one dog (No. 10), atrial ectopy occurred at a very low cumulative dose (40 mg/m²) and preceded ventricular dysrhythmia. Also, in contrast to ventricular dysrhythmia, ectopic atrial rhythms were transient.

A-V Block

Second-degree A-V block occurred in two high-dose (Nos. 3 and 4) and in two low-dose (Nos. 6 and 8) dogs (table 1 and fig 3). In each instance, the block was manifested by sudden, unexpected failure in A-V conduction of one sinus impulse without

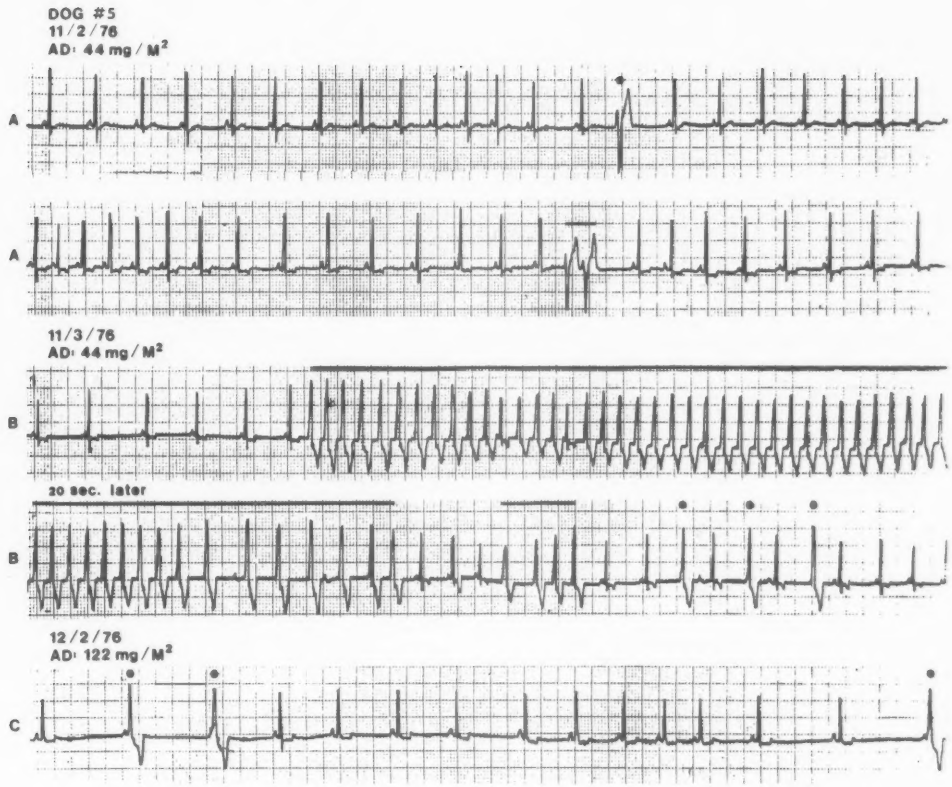

FIGURE 4.—Selected sequential Holter rhythm strips to show multifocal VPCs and paroxysmal rapid ventricular tachycardia in a representative low-dose dog (No. 5). Dates and cumulative drug dosage are indicated. Black dots and bars = isolated ventricular ectopic beats and repetitive ventricular firing respectively. Earliest observed ventricular ectopic activity consisted of isolated and paired PVCs (panel A) and paroxysms of rapid ventricular tachycardia (peak rates, 300/min) (panel B). Differences in QRS contour between ventricular ectopic beats in panels A and B suggest multifocal sites of origin. Accelerated ventricular escape rhythms appeared shortly thereafter and persisted as the dominant ectopic rhythm to the end of the study (panel C). *See* text for details.

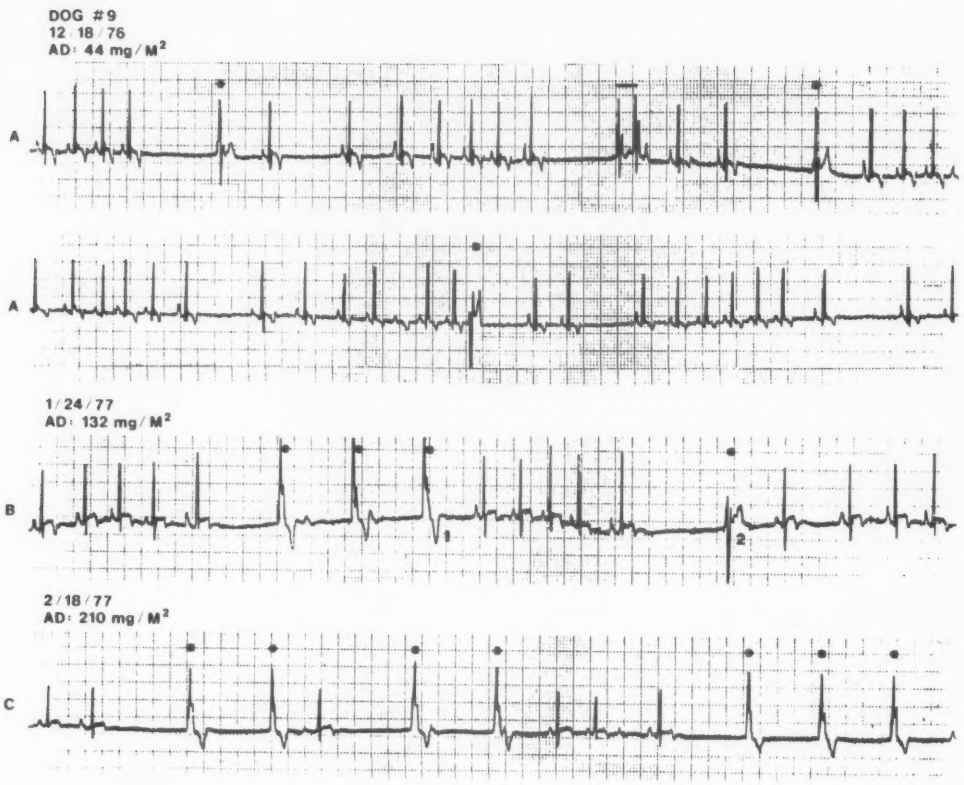

FIGURE 5.—Selected sequential Holter monitor rhythm strips to show development of multifocal accelerated ventricular escape rhythms as well as isolated VPCs in a representative low-dose dog (No. 9) during a 2-mo observation period. Dates and cumulative ADM doses are indicated. Panel A shows a pronounced sinus arrhythmia, the longest cycles of which are closed by accelerated ventricular escapes (top strip: 1st, 2nd, and 4th ectopic beats) from a focus firing at a peak rate of 56–60/min. Panels B and C show the gradual acceleration of the ectopic rate to peak values of 70/min and the appearance of brief runs of slow ventricular tachycardia. Also note that the escape beats have become multiform (panel B, see beats designated 1 and 2). In addition to accelerated escape type beats, scattered, multiform (2 types), early VPCs also developed (panel A). The incidence of early VPCs did not increase during the remainder of the study period and repetitive ventricular tachycardia did not develop. *See* text for details.

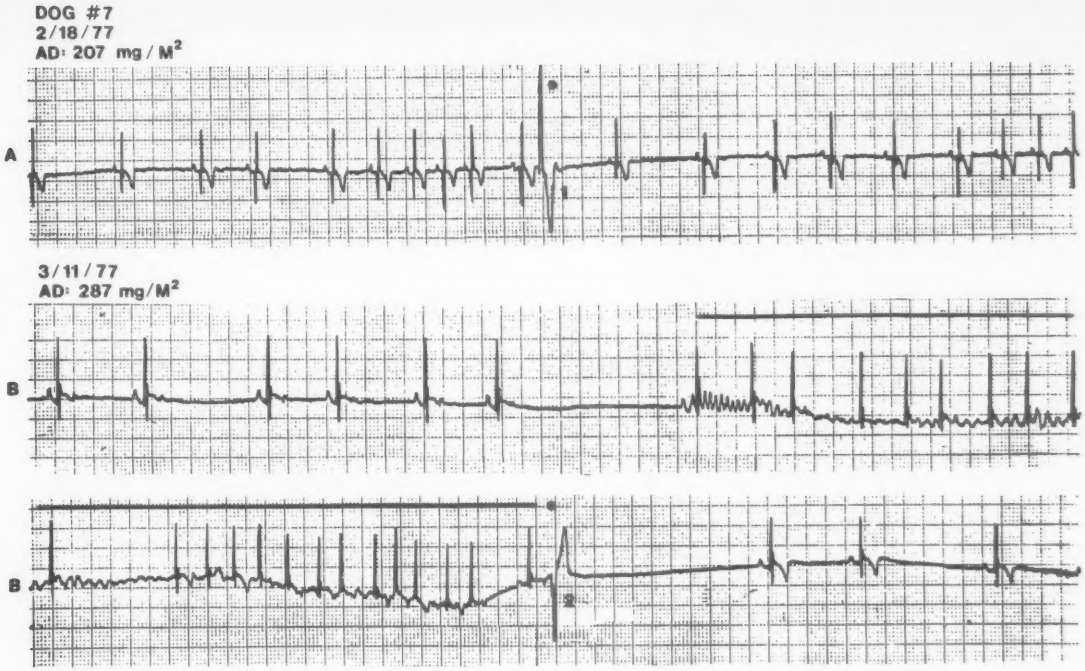

FIGURE 6.—Sequential records, obtained 3 wks apart, to show development of atrial dysrhythmia in a low-dose dog (No. 7). Dates and cumulative drug dosages are indicated. Panel A shows earliest ectopic activity, consisting of isolated VPCs (beat designated by black dot and numeral 1). Panel B shows paroxysmal atrial fibrillation (beats designated by horizontal bar). Paroxysms were both preceded and followed by isolated APCs (not shown). This dog also developed multifocal VPCs (compare VPC 1 and 2 in strips A and B respectively) as well as isolated accelerated ventricular escapes and slow ventricular tachycardia (not shown). In general, appearance of atrial dysrhythmia was associated with more prolonged course of drug therapy and high cumulative dose levels. *See* text for details.

FIGURE 7.—Monitor rhythm strip showing an isolated instance of Mobitz II second-degree A-V block in a high-dose dog (No. 4). Nonconducted sinus P wave is indicated by black dot. Note that conduction failure is sudden without evidence of P-R prolongation of preceding or subsequent P waves. This was also typical of A-V block in low-dose dogs. *See* text for details.

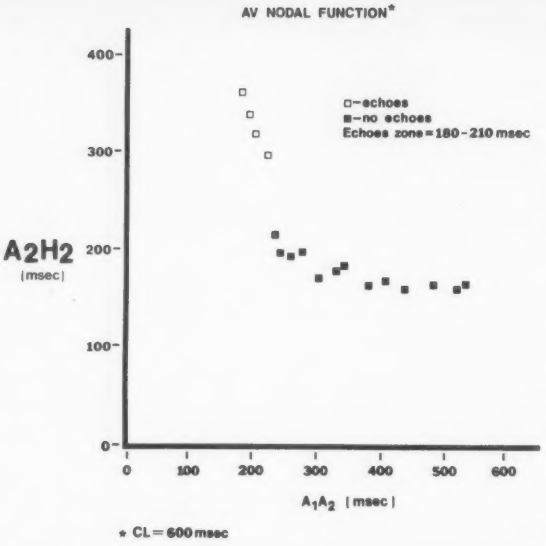

FIGURE 8.—Discontinuous A-V nodal refractory curves obtained from low-dose dog 8 during atrial extra-stimulus testing. The atria were stimulated at a constant cycle length of 600 msec. After every 8th driven beat (A_1), an atrial extra-stimulus (A_2) was introduced at progressively shorter coupling intervals (A_1A_2 intervals, in msec, on abscissa). A-V nodal conduction time for each premature depolarization, ie, time from right atrial to His bundle activation (A_2H_2 interval) is indicated, in msec, on the ordinate. Note that shortening of A_1A_2 interval is associated with gradual prolongation of A_2H_2. At a critical A_1A_2 interval of 180 msec, a marked jump in A_2H_2 time occurs, suggesting a shift in conduction from a now refractory, fast A-V nodal pathway (lower data points) to a second and more slowly conducting A-V nodal pathway (upper data points) (12). If conduction along the second pathway is sufficiently slow to permit prior recovery of the refractory fast pathway, the propagating impulse can "re-enter" the latter and retrogradely excite the atria, with resultant production of echo beats. A_1A_2 intervals resulting in echoes are indicated by open squares. Given that this type of refractory curve is thought to predispose to re-entrant supraventricular tachyarrhythmias (12), it is pertinent that dog 8 developed paroxysmal atrial fibrillation. *See* text for details.

accompanying changes in P-R of conducted beats preceding or following the blocked P wave (fig 7). The block was generally transient. There was no evidence of first-degree or advanced A-V block. Dog 8 also developed a nonspecific intraventricular conduction defect (IVCD) and exhibited prolongation of the H-V interval on electrophysiologic study (*see* below). In high-dose dogs, A-V block appeared on the second day of infusion and after total cumulative doses of 160 mg/m². In low-dose dogs, A-V block tended to appear late during the course of therapy (dog 6, 140 days; dog 8, 133 days) and at relatively high cumulative doses (dog 6, 270 mg/m²; dog 8, 271 mg/m²). This was also true for the IVCD.

Electrophysiologic Studies

Electrophysiologic studies were carried out on one high-dose (No. 4) and three low-dose (Nos. 5, 7, and 8) dogs to confirm the ventricular origin of beats designated as ventricular ectopic beats and to provide further insight into the mechanisms of other ADM-induced abnormalities of cardiac electrical activity. With respect to the former, in three animals exhibiting ventricular ectopic beats during electrophysiologic study, absence of a His potential preceding the QRS complex of such beats confirmed a site of origin in the distal His-Purkinje system.

With respect to the other electrophysiologic parameters studied (table 2), there were no significant differences between treated and control animals insofar as atrial, A-V nodal, His-Purkinje, and ventricular refractory periods were concerned. One low-dose dog (No. 8) did, however, demonstrate discontinuous A-V nodal refractory curves during atrial extra-stimulus testing (fig 8). In addition, introduction of very early atrial premature stimuli during extra-stimulus testing resulted in the development of either atrial or A-V junctional echo beats.

Of the four dogs studied, three (dogs 4, 5, and 7), including one in which transient second-degree A-V block developed (dog 4), did not demonstrate impairment of A-V conduction as evidenced by normal A-H (60–100 msec) and H-V (25–30 msec) intervals over a wide range of cycle lengths (240–600 msec). In the fourth dog (No. 8), in which, in addition to transient second-degree A-V block, an intraventricular conduction defect also appeared, the H-V interval was prolonged to 40 msec (table 2).

S-A nodal function, as assessed by determinations of sinus node recovery time and sino-atrial conduction time in conjunction with rapid atrial pacing and extra-stimulus testing, did not differ from normal (table 2).

Rapid atrial and ventricular pacing and extra-stimulus testing did not result in production of sustained atrial or ventricular tachyarrhythmias in either high- or low-dose dogs. However, brief runs of paired VPCs and ventricular bigeminy occurred following termination of rapid atrial pacing in two low-dose dogs (Nos. 5 and 8). These phenomena were not observed under control conditions.

ECG Contour and Interval Changes

There is suggestive evidence that the development of changes in QRS morphology, particularly amplitude, and in ST-T waves may be of prognostic import with respect to cardiomyopathy (13) and sudden death (5) respectively. Assessment of ECG contour and interval changes during this study did

TABLE 2.—In vivo electrophysiologic data in control and ADM-treated dogs*

Dog No.	SNRT† (msec)	Atrium FRP‡ (msec)	Atrium ERP§ (msec)	A-V node FRP‡ (msec)	A-V node ERP§ (msec)	Ventricle FRP‡ (msec)	Ventricle ERP§ (msec)	A-V conduction 2° block rate	A-V conduction H-V¶ (msec)
Control	820	190	170	< 220	< 190	180	170	280 beats/min	25
4	660	190	170	< 240	< 190	210	200	280 beats/min	30
5	710	160	150	< 210	< 160	170	160	300 beats/min	25
7	900	180	170	< 270	< 190	180	170	260 beats/min	30
8	790	210	190	< 270	< 210	220	200	210 beats/min	40

*In all of the dogs, A-V refractory periods were limited by the achievement of complete atrial refractoriness. The only significant differences between the treated and control dogs were seen in dog 8 which had a lower second-degree A-V block rate (210 beats/min) and H-V prolongation to 40 msec. *See* text for details.

†SNRT = sinus node recovery time.

‡FRP = functional refractory period.

§ERP = effective refractory period.

¶H-V = interval between His bundle deflection and point of earliest ventricular activation on simultaneous surface lead.

TABLE 3.—ECG* intervals in low-dose dogs†

Dog No.	Date	ADM‡ (mg/m²)	P-R	QRS	Q-T
5	10/26/76§	0	0.07	0.05	0.15
	11/3/76	44	0.08	0.05	0.15
	12/2/76	122	0.08	0.05	0.15
6	12/2/76§	0	0.08	0.05	0.21
	3/30/77	173	0.10	0.04	0.21
	4/1/77	197	0.09	0.05	0.22
	4/26/77	270	0.09	0.04	0.21
7	12/10/76§	0	0.08	0.04	0.16
	3/17/77	286	0.12	0.05	0.20
	4/21/77	310	0.10	0.04	0.16
8	12/10/76§	0	0.07	0.04	0.16
	3/11/77	200	0.07	0.06	0.16
	5/6/77	271	0.07	0.10	0.20
9	12/13/76§	0	0.10	0.05	0.21
	3/30/77	184	0.09	0.05	0.20
	4/27/77	251	0.10	0.05	0.21
10	12/13/77§	0	0.12	0.04	0.22
	2/18/77	216	0.12	0.05	0.21
	3/2/77	247	0.12	0.05	0.22

*ECG intervals indicated in secs and determined for cycle length of 600 msec.

†Average values for P-R, QRS, and Q-T ECG intervals obtained from Holter monitor records for the 6 low-dose dogs during the pre-drug control period and at selected intervals during the course of ADM treatment. All measurements were made for cycle length (600 msec) equivalent to a rate of 100/min. *See* text for details.

‡Cumulative dose at time of measurement.

§Control values prior to institution of ADM.

not reveal systematic changes in any of the observed variables in either group of dogs compared with pretreatment control values (table 3). More specifically, there were no consistent alterations in frontal plane axis, QRS contour or amplitude, and Q-T interval, defined at a constant cycle length equivalent to a rate of 100/minute, with the sole exception of low-dose dog 8 that developed a nonspecific intraventricular conduction defect, the QRS increasing from 700 to 1000 msec in duration. The P-R of conducted sinus beats was similarly unaffected even in dogs exhibiting transient second-degree A-V block. The ST-T was also apparently unaffected with the observed variations being comparable to those noted on pretreatment control records.

Blood Pressure Changes

Since sudden death has occurred during ADM infusion, the possibility that it could have been

TABLE 4.—Comparisons between occurrence of dysrhythmia in the 6 low-dose dogs and histologic findings from light and electron microscopic studies on selected specimens of heart muscle from different sites from the same dogs*

					Pathology§			
		Dysrhythmia‡			Light microscopy			Electron microscopy
Dog No.	ADM† (mg/m²)	Atrial	Ventricular	A-V block	Atrium	Ventricle	His-Purkinje system	Ventricle
5	122	(–)	(+)	(–)	ND	ND	ND	0
6	270	(+)	(+)	(+)	+	0	0	ND
7	310	(+)	(+)	(–)	++	+++	+	+++
8	271	(+)	(+)	(+)	++	+++	+	+++
9	251	(–)	(+)	(–)	+	0	0	0
10	247	(+)	(+)	(–)	++	+++	+	ND

**See* text for details.

†Cumulative dose at time of death.

‡(+) = dysrhythmia present; (–) = dysrhythmia absent.

§0 = normal myocardium, no ADM effect; + = occasional sparse vacuolated myocytes only; ++ = moderate No. of focal myocytes showing vacuolization and/or myofibril loss; +++ = many diffusely affected myocytes showing vacuolization and/or myofibril loss; ND = no data, histology not done.

related to acute changes in blood pressure was considered. Blood pressure was therefore monitored before, during, and for variable periods after drug infusion in all high- and one low-dose dog(s) (fig 1). Within 5 minutes of the start of infusion, all high-dose dogs exhibited a pronounced fall in the mean arterial pressure (average decline, 42%) which was maximal at about 30 minutes and thereafter returned gradually to control levels. Full restoration required up to 90 minutes. In the one low-dose dog studied, the fall in the mean arterial pressure was less pronounced, reaching a maximum of 21%. Restoration was also more prompt, with initial levels being reached by 40 minutes.

Histologic Studies

Possible correlations between the character and severity of the observed dysrhythmias and the development of cardiomyopathy were assessed by histologic studies, using light and electron microscopic techniques, on specimens of atrial and ventricular muscle and specialized ventricular conducting tissues (His-Purkinje system) in the low-dose group (dogs 5–10).

Histologic findings are summarized in table 4. Observed dysrhythmias and cumulative drug dosages at the time of death are also tabulated. It will be seen that only one dog (No. 5) failed to exhibit any evidence of ADM-induced myocardial injury. This dog also received the lowest cumulative drug dose (122 mg/m²). In addition, histologic studies were confined to ventricle, the atrium and His-Purkinje system not being specifically examined. All other animals (dogs 6–10) exhibited signs of cellular injury. There was, however, marked individual variability with respect to both the magnitude and distribution of the observed changes. In two animals (dogs 6 and 9), cellular changes were quite minimal, being limited exclusively to the atrium. Ventricular or His-Purkinje system involvement was not demonstrated. On the other hand, the three remaining dogs (Nos. 7, 8, and 10), including both beagles (Nos. 7 and 8), exhibited diffuse cardiac involvement, the most severe changes (+++) centering in ventricular myocardium. The atrial myocardium and His-Purkinje system were also involved but to a lesser extent (++ and + respectively). Variability in the extent and distribution of involvement was particularly striking since all five dogs had received more or less equivalent cumulative drug doses (247–310 mg/m²) over a comparable timespan (18–20 weeks). This individual variability in response is in accord with findings in man (14). There were no clear-cut pathologic differences between beagles and mongrel pound dogs.

Although all dogs exhibiting histologic evidence of cellular injury also exhibited dysrhythmia, no consistent correlations were noted between the nature and severity of the rhythm disturbances and the pathologic changes. Correlations were best with respect to atrial dysrhythmia, both dogs manifesting atrial fibrillation (dogs 7 and 8) also demonstrating evidence of moderate injury to atrial tissue.

The correlations between histologic evidence of injury to the specialized conducting system and A-V conduction disturbances were even less consistent. Of the three dogs in which histologic abnormalities of the specialized conducting tissues were found (dogs 7, 8, and 10), only one (dog 8) exhibited ECG

evidence of A-V conduction impairment. This dog, which developed both transient second-degree A-V block and a late intraventricular conduction defect, was also found to have prolongation of the H-V interval during electrophysiologic studies. Conversely, dog 6, the second of the two low-dose animals to develop transient second-degree A-V block, did not exhibit pathologic changes in the specialized conduction system.

Disparities between rhythm and pathologic change were particularly pronounced for ventricular dysrhythmias. For example, dog 10, despite evidence of diffuse cardiomyopathic changes, including involvement of both specialized conducting tissues and ventricular myocardium, manifested only scattered, isolated VPCs. In contrast, none of the three dogs that developed ventricular tachycardias (dogs 5, 6, and 9) exhibited pathologic abnormalities in ventricular myocardium. There was also no evidence of histologic injury to the specialized conducting system in the two dogs whose tissues were examined (dogs 6 and 9).

DISCUSSION

Experimental studies on ten dogs showed that ADM administration was consistently associated with significant alterations in heart rate and blood pressure and with development of potentially harmful ectopic atrial and ventricular dysrhythmias and A-V block. The occurrence of dysrhythmia was not clearly dose-dependent. In addition, there were no consistent correlations between the nature and severity of dysrhythmia and morphologic indices of cardiomyopathy.

Heart Rate and Blood Pressure

With respect to heart rate and blood pressure effects, ADM infusion consistently resulted in prolonged periods of sustained sinus tachycardia and transient hypotension, the average reduction in mean arterial blood pressure ranging between 21% and 42%. The magnitude and duration of hypotension were dose-related, the most pronounced changes occurring in the high-dose dogs. Whether this phenomenon was related to an abrupt decrease in peripheral vascular resistance or to depressive effects on myocardial contractility cannot be determined from our study. Other available evidence is also equivocal. On the one hand, some experimental studies show that ADM infusion is often associated with transient reduction in coronary blood flow and depression of left ventricular function, the latter assessed in terms of changes in dP/dt (15). These data suggest that the decrease in arterial pressure may be explicable, at least in part, in terms of an acute depression of ventricular performance mediated by inadequate myocardial blood flow. On the other hand, there also are clinical (16) and animal[5] studies which have focused on the occurrence of diffuse urticarial type eruptions in conjunction with ADM infusion. The fact that both the cutaneous reaction and the hypotension could be partially blocked by pretreatment with antihistaminic agents[5] indicates that the hypotension may be on a vascular basis and mediated by release of histamine or other vaso-active peptides.

The persistence of sinus tachycardia for several hours following normalization of blood pressure, which has also been observed by others (15), may have represented reflex efforts to maintain cardiac output in the face of depressed myocardial function or be related to high levels of circulating catecholamines which have been reported to occur in dogs following ADM infusion (15,17). Findings in Langendorf perfused hearts that β-adrenergic blockade with propranolol abolished the chronotropic response to ADM (18) are also in accord with conclusions that the increase in sinus rate reflects enhanced sympathetic activity.

The occurrence of comparable hemodynamic and chronotropic alterations in man could be a factor underlying sudden death during ADM therapy in selected patients. Patients with significant coronary artery disease might be expected to be at particular risk. For example, Ugoretz (19) described a patient who died suddenly within minutes after initiation of ADM infusion. An autopsy revealed extensive triple vessel coronary artery disease with the result that death was thought to be only coincidentally related to the drug. In such patients, however, the combination of hypotension, sustained sinus tachycardia, and reduced coronary blood flow could well have resulted in extensive myocardial ischemia and initiation of a lethal dysrhythmia. Findings by Lefrak et al (20) of transient, pronounced ST segment elevation in a patient 3 hours after ADM infusion provide additional support for the occurrence of drug-related alterations in coronary blood flow with resultant myocardial ischemia and depression of left ventricular function.

Rhythmogenic Activity

Of even greater interest with respect to the occurrence of sudden death during ADM therapy was the high incidence of potentially harmful ectopic atrial

[5]Page J. Personal communication. Adria Laboratories, Wilmington, Del.

and ventricular dysrhythmias and of A-V and I-V conduction disturbances which developed in dogs exposed to this agent. Occurrence of persistent ventricular dysrhythmias in 50% of the short-term high-dose and in 100% of the long-term low-dose dogs, including ventricular tachycardia in 25% and 83% of these groups respectively, is particularly relevant.

Consideration of ADM-induced ventricular dysrhythmias from a mechanistic point of view indicates that this agent exerts multifaceted electrophysiologic actions. More specifically, of the two general varieties of ventricular dysrhythmia, ie, slow and fast ventricular tachycardia, the former exhibited characteristics typical of an accelerated escape rhythm of the type best explained in terms of enhanced automaticity of latent pacemaker cells in the His-Purkinje system (21), the increase in escape rate over time and eventual appearance of multifocal activity reflecting acceleration of spontaneous depolarization rates of such cells and an increase in the sites of involvement respectively. Preliminary findings from in vitro glass microelectrode studies on isolated specimens of dog Purkinje fiber and papillary muscle indicating that ADM appears to enhance automaticity of latent pacemaker cells in the His-Purkinje system are pertinent in this regard (22).

Characteristics of the rapid ventricular tachyarrhythmias, on the other hand, suggested a re-entrant type mechanism. Re-entrant phenomena are thought to be dependent on localized conditions which predispose to slow and inhomogeneous conduction and fragmentation of excitation (23). Findings from in vitro electrophysiologic studies showing that exposure to ADM can, in addition to enhancing automaticity, also cause lowering of resting potential, marked but frequently quite variable increases in Purkinje fiber action potential duration, and depressed conduction and oscillatory activity (Singer DH, unpublished observations), support conclusions that this agent could give rise to re-entrant as well as accelerated automatic ventricular rhythms.

The fact that 75% (three of four) of the dogs that developed rapid ventricular tachycardias also exhibited A-V or intraventricular conduction disturbances (table 1) provides additional evidence for a re-entrant type mechanism as do in vivo electrophysiologic studies. With respect to the latter, dog 8, which developed rapid ventricular tachycardias together with Mobitz II second-degree A-V block and an intraventricular conduction disturbance during drug treatment (table 1 and fig 3), also exhibited coupled VPCs and runs of ventricular bigeminy in conjunction with rapid atrial pacing studies, a finding which has been attributed to unconcealment of potential re-entrant pathways by cycle length dependent increases in refractoriness (24). The latter, in turn, is thought to predispose to repetitive ventricular firing (11). The same dog also exhibited discontinuous A-V nodal refractory curves suggestive of dual A-V nodal pathways (fig 8) and supraventricular echoes at short coupling intervals during extra-stimulus testing. These findings, which were not noted under control conditions, might be expected to facilitate development of re-entrant supraventricular tachyarrhythmias (12). It is of interest that this dog developed atrial fibrillation in addition to ventricular tachyarrhythmias.

The diffuseness and multiplicity of ADM effects on electrical activity in all parts of the heart underscore its rhythmogenic potential.

Possible Cellular Mechanisms of ADM Action

The cellular mechanisms whereby ADM exerts its electrophysiologic and pathologic effects are not yet clearly defined. A number of studies have shown that myocardial cells exposed to ADM exhibit impaired incorporation of precursors into DNA, RNA, and cellular proteins (25,26). Gradual depletion of essential structural proteins or enzymes caused by this represents one possible explanation for the observed phenomena. Other studies (27) have suggested that cellular injury may be related to drug-induced inhibition of coenzyme Q_{10}-dependent electron transfer reactions, thereby uncoupling oxidative phosphorylation. More recently, Handa and Sato (28) have shown that when microsomes are exposed to anthracycline compounds, super-oxide radical ions are formed which cause conversion of membrane-bound unsaturated fatty acids to lipid peroxides. Such changes in membrane composition could, in turn, cause functional alterations leading to cellular injury and dysrhythmia. A possible role for super-oxide formation in the genesis of ADM cardiomyopathy is further supported by the findings of Myers et al (29) showing that the free radical scavenger, tocopherol, may markedly increase drug concentrations required to cause cardiomyopathy in mice without a corresponding decrease in antineoplastic activity. Tocopherol effects on the electrophysiologic sequelae of ADM therapy are currently under study.

Pathologic Correlates

It is tempting to consider arrhythmogenesis as part of the total spectrum of changes associated with the development of ADM cardiomyopathy. Examination of possible relationships between the occurrence of dysrhythmia and cardiomyopathy revealed good overall correlations, all five dogs in

which histologic abnormalities were found exhibited rhythm disturbances (table 4). Conversely, five of the six dogs exhibiting dysrhythmia also demonstrated signs of cellular injury (table 4). Dog 5, the one animal in which pathologic changes were not observed, received the lowest cumulative dose (122 mg/m^2) over the shortest timespan (8 weeks) of any member of the group. In addition, histologic studies were quite limited, being confined solely to ventricular myocardium.

At this time our material does not permit clear-cut correlations between the severity of dysrhythmia and its specific types (ie, atrial dysrhythmia, ventricular dysrhythmia, A-V block, etc) *and* the extent and geographic distribution of pathologic changes. Insofar as can be determined from available data, the relationships were much less consistent (table 4). This is not surprising given the frequently patchy nature of histologic changes (6, 30), a problem compounded by the limited amount of heart tissues which had been examined at the time of this writing and by the inability of intermittent monitoring techniques to detect all arrhythmic episodes. Histologic studies are continuing.

Comparisons between the time course of development of dysrhythmia and of cardiomyopathy also support conclusions that they reflect the same basic patho-physiologic processes. For example, ventricular ectopy, the principal type of rhythm disturbance, did not occur in conjunction with short-term drug administration but took weeks to months to appear. Once established, ventricular dysrhythmias persisted and became progressively more severe over time. The delayed onset and gradual progression of the dysrhythmia were qualitatively similar to the time course of development of cardiomyopathy (6), differing primarily in terms of an earlier onset and rapid progression. The uniform occurrence of ventricular ectopy in all animals receiving long-term treatment and its earlier onset relative to other manifestations of cardiomyopathy are of great interest because they suggest that ventricular dysrhythmia may represent a very early sign of ADM-induced cardiomyopathy.

CONCLUSIONS

Although adherence to strict limitations on ADM dosage schedules has minimized the likelihood of severe congestive cardiomyopathy (13), a number of important questions concerning other possible cardiotoxic complications of drug therapy remain unanswered. These include: (*a*) the drug's rhythmogenic activity and the extent to which dysrhythmia may underlie the increased incidence of sudden death in ADM-treated patients; (*b*) the nature and magnitude of hemodynamic changes associated with ADM infusion which might render its use potentially harmful; and (*c*) the existence of sensitive indicators of ADM cardiotoxicity, use of which would facilitate increased individualization of therapeutic regimens.

Data from experimental dog studies described in this report appear to provide some insight into these matters. First and foremost, the near universal development of ventricular dysrhythmias, alone or in combination with supraventricular tachyarrhythmias and/or atrioventricular and intraventricular conduction disturbances, in treated dogs serves to underscore arrhythmogenesis as a major cardiotoxic effect of ADM. The frequent findings of repetitive ventricular firing, including bouts of paroxysmal rapid ventricular tachycardia, represent a particular concern, and would provide a ready explanation for the increased incidence of sudden death seen in conjunction with ADM therapy. Development of A-V block in ADM-treated dogs represents a second area of concern, suggesting the possibility that drug-induced accentuation of preexisting conduction delays may result in advanced A-V block and bradyarrhythmia. Lack of consistent correlations between the onset of dysrhythmia and either drug dosage or duration of therapy emphasizes the need for frequent monitoring of patients with respect to these complications. Second, the marked increase in sinus rate and arterial hypotension seen in conjunction with drug infusion represents additional potentially harmful effects, particularly in patients with significant coronary disease. In such patients, these could precipitate serious myocardial ischemia, and thereby result in myocardial infarction or life-threatening dysrhythmia. Finally, the fact that ventricular dysrhythmias generally made their first appearance at lower cumulative drug dosages than is generally true for cardiomyopathy (6) suggests that arrhythmia may serve as an early warning sign of ADM-induced myocardial injury. Proper use of such an index might facilitate greater individualization of therapeutic regimens, avoiding the need for invasive biopsy techniques (14). Clearly, systematic clinical studies are required to assess the applicability of these dog findings to man.

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Epilogue

This meeting was convened with the hope that we might more adequately define the nature of the anthracycline-mediated cardiomyopathy and provide clinicians with a reliable method for assessing its magnitude. Unfortunately, we have only partially succeeded.

Several participants in this meeting have shed important new light on the nature of the process. There are two particularly important implications of the endocardial biopsy series reported here by the Stanford group. First, while only a small minority of patients receiving adriamycin (ADM) develop overt congestive heart failure, an overwhelming majority of all patients receiving a full 550-mg/m^2 dose of this drug have pathologically significant cardiac damage. Second, these changes are apparent early, after only a few doses of ADM have been administered. The linear relation between the cumulative ADM dose and the degree of pathology seen suggests that in most patients a constant amount of cardiac tissue is damaged with each dose of the drug. Additional light is shed on this process by the work of Dr. Singer and colleagues (Veterans' Administration Hospital, Seattle, Wash). Their results suggest that an acute wave of cardiac damage, reflected by a drop in ejection fraction, commonly accompanies each dose of ADM. Are the lesions described by the Stanford group the pathologic residual of this acute syndrome? If so, the magnitude of the acute drop in ejection fraction might be of predictive value. It is obvious that we need to know more about both the acute physiologic and pathologic changes which follow ADM administration and what relation these changes have to the chronic cardiomyopathy.

The second purpose of this meeting, which was to define the best approach to monitoring patients for the development of cardiomyopathy, proved less successful. At first glance endocardial biopsy would appear to have much to recommend it. However, a number of difficulties with the approach are now apparent. First, it is currently available in only a few treatment centers and is never likely to become widely available. Second, it involves using a small sample to determine the severity of an essentially focal process. As might be expected, this results in significant sampling errors. In particular, there are a significant number of patients with congestive heart failure whose biopsies only showed mild (grade 1) damage.

Those techniques which monitor cardiac physiologic function also suffer from limitations. The inherent limitations of these techniques are reviewed by Dr. Gottdiener (National Heart, Lung, and Blood Institute, Bethesda, Md). From the papers presented in this issue, it is apparent that the magnitude of the changes observed is small and the variability in the measurements is large. Thus, it becomes difficult to separate the healthy from the diseased heart and certainly difficult to pick up early changes. The difficulty with all of these studies may be that they have attempted to study cardiac function at rest. It would seem logical that the ability of the heart to augment its output in response to exercise would make a sensitive measure of a developing cardiomyopathy. Perhaps techniques such as electrocardiogram-gated scintiangiography used in conjunction with exercise will finally provide us with a sensitive, noninvasive method for quantitating this cardiomyopathy.

Charles E. Myers

National Cancer Institute
Bethesda, Md

ANNOUNCEMENTS

III Chemotherapy Foundation Symposium on "New Developments and Changing Concepts in Cancer Chemotherapy"

New York, New York, October 27 and 28, 1978

The Division of Medical Oncology, the Department of Medicine, the Department of Neoplastic Diseases, and the Page and William Black Post-Graduate School of Medicine of the Mount Sinai School of Medicine will present the III Chemotherapy Foundation Symposium on "New Developments and Changing Concepts in Cancer Chemotherapy" to be held at the Barbizon Plaza in New York on October 27 and 28, 1978. Panelists include leading US and foreign investigators.

For registration information contact: Dr. Ezra M. Greenspan, Page and William Black Post-Graduate School, Mount Sinai School of Medicine, 1 Gustave L. Levy Place, New York, NY 10029.

Medical Oncology Fellowships

There are openings for a 2-year clinical-research program starting in July 1979 in major teaching hospitals of the Tufts University School of Medicine. *For information contact:* L. Nathanson, MD, Chief, Medical Oncology, Tufts/New England Medical Center Hospital, 171 Harrison Ave, Boston, Mass 02111.

2nd International Conference on the Adjuvant Therapy of Cancer

Tucson, Arizona, March 28–31, 1979

The 2nd International Conference on the Adjuvant Therapy of Cancer will be held in Tucson, Arizona, March 28–31, 1979, under the sponsorship of the Cancer Center Division of the University of Arizona. Drs. Sydney E. Salmon and Stephen E. Jones will serve as Conference Co-Chairmen. The deadline for submission of abstracts (prepared in the format of The American Association of Cancer Research and American Society of Clinical Oncology) is December 1, 1978.

For further information write to: Ellen Gerrity, Conference Coordinator, Cancer Center Division, University of Arizona, Tucson, Ariz 85724.

23rd Annual Clinical Conference on "Cancer of the Genitourinary Tract"

Houston, Texas, November 2–3, 1978

The University of Texas System Cancer Center, M.D. Anderson Hospital and Tumor Institute in Houston, announces the 1978 Clinical Conference on "Cancer of the Genitourinary Tract" to be held at the Shamrock Hilton Hotel, Houston, Texas, November 2–3, 1978. This Conference will focus on issues of diagnosis, staging, and therapy as they relate to the critical and sometimes controversial therapies of the multiple stages of urologic malignancies. The Conference will be jointly sponsored by The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, and the American Cancer Society, Texas Division, Inc. It will provide practicing primary care physicians, oncologists, and urologists with critical issues at the moving edge of therapeutic investigation on urologic malignancies. An opportunity will be provided for speakers and registrants to exchange information at the conclusion of each session. There will be a registration fee.

This medical-education offering meets the criteria for 14 hours in Category I of the Physician's Recognition Award of the American Medical Association. This program is also acceptable for 14 prescribed hours by the American Academy of Family Physicians.

For additional information write: George R. Blumenschein, MD, Office of Education, The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, Texas Medical Center, Houston, Tex 77030.

Conference on "Combined Modalities: Chemotherapy/Radiotherapy"

Hilton Head, South Carolina, November 15–18, 1978

The Committee for Radiation Oncology Studies, in conjunction with members of the Radiation Study Section and leading oncologists and with the support of the National Cancer Institute, is sponsoring a conference on the interaction of chemotherapy and radiotherapy. The meeting will focus on experimental results of laboratory and clinical studies of the interaction of selected cancer chemotherapeutic agents and radiation. The emphasis will be on the response of both normal and tumor tissues.

Attendance will be limited to people working in the field, certain invited speakers and participants, and those investigators who submit abstracts that are accepted by the organizing committee. It is intended to be a workshop-type meeting and abstracts will be presented either in open session or as poster-scientific exhibit sessions.

Data to be presented at the meeting should meet the following criteria: (*a*) data should not have been published previously; (*b*) data must be relevant to the subjects of the meeting listed below, and (*c*) a paper must be prepared and submitted for publication at the time of the meeting, whether to be presented as an exhibit or oral presentation. The deadline for submission of abstracts will be August 1, 1978. Persons desiring to attend and whose abstracts are accepted will be eligible for partial travel support to the meeting. Additional details as to the format of the papers will be sent to those proffering accepted abstracts.

The research to be reported will include pharmacology, biochemistry, and basic chemical effects of the specific compounds, in vitro results with interaction of drug and radiation, in vivo normal tissue response to drug and radiation, and current clinical trial information. The following drugs are of special interest: bleomycin, adriamycin, cyclophosphamide, *cis*-platinum, and nitrosoureas. Papers on other agents will be considered for a session on other interesting and new agents. In addition to inviting the submission of abstracts, the organizing committee also invites nominations of young investigators who will be supported for travel to the meeting and who will not necessarily be presenting a paper.

For further details on the meeting and for abstract forms, write to: Theodore L. Phillips, MD, Chairman, Organizing Committee, Division of Radiation Oncology, University of California, M-330, San Francisco, Calif 94143.

Seminars on Oncology at Roswell Park Memorial Institute

Buffalo, New York

On September 8, 1978, there will be a seminar on "New Leads in Cancer Therapeutics" organized by the Department of Experimental Therapeutics (Dr. Enrico Mihich, Chairperson) and on October 11 and 12, 1978, there will be a seminar on "Adjuvant Therapy in Solid Tumors" organized by all Clinical Departments (Dr. H. James Wallace, Jr, Chairperson) at Roswell Park Memorial Institute.

There is a $25.00 fee for the 1-day seminar and a higher fee for the longer program. *For further information contact:* Ms. Claudia Lee, Cancer Control, Roswell Park Memorial Institute, 666 Elm St, Buffalo, NY 14263.

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